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DISSECTING ANEURYSM

A STUDY OF SIX RECENT CASES*

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IT IS our purpose in this paper to report six recent cases of dissecting aneurysm which were studied at the bedside, and to focus attention upon certain diagnostic criteria and problems which the study of these cases has emphasized. Only a few years ago, dissecting aneurysm was seldom recognized clinically. The disease was usually misdiagnosed as ruptured peptic ulcer, cerebral thrombosis, arterial embolism, and, in the last decade, as coronary occlusion. In recent years, however, observations by Hamman and Apperley,[1] Weiss,[2] Tyson,[3] and others[4-10] have led to a better understanding of the clinical and pathologic manifestations of dissecting aneurysm, and in a number of cases the diagnosis has been made during life.

The chief signs and symptoms which have been described by most recent writers are severe substernal or epigastric pain, radiating to the back, neck, lumbar region, legs, and, rarely, to the arms; syncope; history of a previously existent hypertension; inequality or obliteration of peripheral pulses, with the sequelae of impaired circulation in the organ or region formerly supplied by the obliterated vessel; and an aortic diastolic murmur, often with the peripheral signs of aortic insufficiency. There may be slight fever, and leucocytosis, frequently as high as 20,000, is usually present. The electrocardiogram ordinarily shows no abnormality, but cases have been reported in which the tracings simulated those seen in coronary occlusion.[11, 12, 13] Death usually occurs within a few hours or days. Occasionally, a patient lives for weeks or months or dies of some unrelated disease years after the dissecting aneurysm has been endothelialized and "healed."

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CASE 1.—C. G. H. 64331. The patient, a white man 56 years old, was admitted to the hospital Nov. 12, 1936, complaining of severe epigastric and precordial pain of nine hours' duration. During the previous afternoon, after a paroxysm of coughing, he was suddenly seized by a severe knifelike pain in the epigastrium that penetrated to the back, ascended into the chest, and radiated down both arms. He became so weak that he would have fallen had he not been supported. Although the pain soon abated, it kept him awake until two o'clock the next morning, when its intensity increased so much that he left his bed to search for a doctor. On his way down the street he collapsed, and was found by the police in an unconscious state. There was no history of syphilis, rheumatism, chorea, or of previous precordial pain. His blood pressure had never been taken previously. The cardiorespiratory history was negative, as was the remainder of the past history.

On admission the patient complained of "soreness" in the epigastrium, chest, and back. His temperature was 98.6° F., his pulse rate 64 per minute, his respiratory rate 22 per minute, and his blood pressure 105/60. He was moderately orthopneic. The radial pulses were of equal volume. The heart appeared to be slightly enlarged, the cardiac sounds were loud, and the heart was beating regularly and slowly. A soft systolic murmur, audible all over the precordium, was loudest at the aortic area; no diastolic murmur was heard. A few râles were heard at the base of the right lung. The abdomen was soft, but there was a point of tenderness over the xiphoid process; the liver was not palpable but seemed slightly enlarged to percussion. There was no peripheral edema.

The erythrocytes numbered 5,000,000 per cubic millimeter, and the leucocytes, 10,700. The hemoglobin content of the blood was 13.8 gm. per 100 c.c. The differential leucocyte count gave the following result: neutrophiles, 77 per cent; eosinophiles, 1 per cent; lymphocytes, 18 per cent; and monocytes, 4 per cent. Examination of the urine showed nothing except the presence of 4 to 6 leucocytes per high-power field. The Kahn test was negative on the blood serum and on the cerebrospinal fluid. Roentgenograms of the chest showed moderate enlargement of the heart; the aorta was very tortuous and elongated, and the descending portion appeared to be moderately dilated. Four serial electrocardiograms showed left axis deviation and a variation in the P-R interval of 0.2 to 0.24 sec. On admission, the T-wave in the Lead I was diphasic; three days later the S-T segment was elevated 0.7 mm. in the same lead, but this slight abnormality did not persist. The T-wave in Lead IV was diphasic on admission but later became inverted.

Five hours after admission, a moderately loud, early diastolic murmur was noted along the left border of the sternum. A diagnosis of dissecting aneurysm was made on the basis of the history and the appearance of this diastolic murmur. At this time the blood pressure was 110/45 in the left arm and 112/46 in the right arm. The radial, femoral, and dorsalis pedis pulses were equal in volume. A greatly increased systolic pulsation was noted in the left common carotid artery, and the patient complained of tenderness along this vessel. On the second day after admission, the diastolic murmur was considerably louder and was easily audible to the right of the sternum in the second intercostal space as well as along the left border of the sternum. The pulse was collapsing, and there was a pistol-shot sound in the femoral arteries. On November 19, eight days after admission, a mid-diastolic murmur was first heard at the apex; this was thought to be an Austin Flint murmur. For the first two weeks morphine was required periodically to give relief from pain, but after that the patient gradually improved and at the end of a month was able to be up in a wheel chair. By this time the tenderness and increased pulsation in the left carotid artery had disappeared. At the end of six weeks he was walking about. The blood pressure was measured on numerous occasions and was found to

average 120/45, with a maximum of 135/65. On December 2 he suffered for the first time from attacks of paroxysmal dyspnea. On December 29 he developed clinical evidence of pulmonary infarction and expectorated bloody sputum. Thereafter he grew worse steadily. Pain beneath the sternum and in the back, combined with moderately severe dyspnea, made his life miserable. He died Jan. 24, 1937, of bronchopneumonia. The murmurs over the heart remained unchanged until the last.

The post-mortem diagnoses* were dissecting aneurysm of the aorta; atherosclerosis of the aorta; cardiac hypertrophy and dilatation with myocardial degeneration; chronic passive congestion of the spleen and liver; chronic cholecystitis and cholelithiasis; and lobular pneumonia. The pericardial sac contained 75 c.c. of serosanguineous fluid. The heart, which was hypertrophied and dilated, weighed 600 gm. There was no organic disease of the valves. The coronary arteries appeared normal. The aorta was markedly dilated throughout. Numerous atherosclerotic plaques, some of which were filled with calcareous deposits, were noted in the intima. Between the sixth and the ninth thoracic vertebrae the aorta was dissected by a large amount of partially clotted blood, splitting the media throughout three-quarters of the circumference of the vessel, namely, the posterior, the left lateral, and the anterior aspects. The dissection apparently had begun in this region, and had extended upward to a point just distal to the sinuses of Valsalva, and downward to the bifurcation of the abdominal aorta. No tear of any kind was found in the intima of the aorta. The intercostal and lumbar arteries were torn across as they traversed the sac. The dissection also extended about 1.5 cm. up the lateral half of the left common carotid artery. Sections through this area showed that the outer portion of the media and the inner part of the adventitia were involved. Most of the blood had been replaced by fibrous tissue, within which were seen many small nerve trunks. Sections through the vessel showed no evidence of its having been occluded. None of the other vessels arising from the aortic arch was involved. The lungs were the seat of bronchopneumonia, chronic passive congestion, and edema. The liver and spleen showed changes characteristic of passive congestion.

Comment.—Although the onset of the disease in this patient was quite typical, the case presents several interesting and unusual features. One of the less common signs of dissecting aneurysm is an aortic diastolic murmur. Resnick and Keefer[5] called attention to this phenomenon in 1925, and in 1933 Hamman and Apperley[1] diagnosed the disease by this means. So far as we have been able to ascertain from the literature, this is the first reported case in which the diastolic murmur has been observed to develop after the onset of symptoms. Inasmuch as some authors,[5, 13] give credence to the theory that these murmurs, as well as the peripheral manifestations of aortic insufficiency, may be caused by the backflow of blood into the aneurysmal sac during diastole, it is significant that in this case there was neither a tear in the intima of the aorta nor any sign of communication of the lumen of the aorta with the aneurysm. Wood, Pendergrass, and Ostrum[10] and Hamman and Apperley[1] have suggested that the explanation lies in a relative insufficiency of the aortic valve caused by dilatation of the ring, following upon dissection of the aortic coat down to the valve cusp. In the present case there is nothing inconsistent with this hypothesis.

*The post-mortem examinations in all of the cases reported herein were performed in the Institute of Pathology of the College of Medicine of the University of Cincinnati.

Though *decrease* in the volume of one or more peripheral pulses is frequently noted in dissecting aneurysm, this patient presented a striking *increase* in the pulse volume of the left common carotid artery with tenderness along the course of the vessel. Inasmuch as this vessel was the only one arising at the aortic arch which was involved in the dissection, this sign takes on added importance. Microscopic examination showed that many nerve fibers were involved in the dissection, and therefore it seems likely that spontaneous periarterial sympathectomy occurred, with a resulting dilatation of the vessel similar to that which follows surgical sympathectomy. The pain and hyperesthesia which accompanied the dilatation and disappeared when the arterial tone was regained likewise may have been brought about by involvement of the arterial nerve plexus. It is of interest that Weiss[2] has suggested that similar involvement of the depressor nerve endings in the aortic arch may be responsible for the syncope of dissecting aneurysm.

CASE 2.—C. G. H. 68188. The patient was a colored male bricklayer, 51 years of age, who was admitted to the hospital on Feb. 7, 1937, complaining of pain in the chest and abdomen of twenty hours' duration. On the day before admission, while crossing the street, he was suddenly stricken with a severe viselike pain in the lower cervical region which radiated to the lower sternal region, into both arms, and down the abdomen. Although he was very weak, he was able to make his way home, where he crawled into bed and soon lost consciousness. He recovered consciousness, only to be harassed by pain, nausea, and vomiting.

Six weeks before the onset of his present illness he had come to the dispensary complaining of lumbago. At this time the blood pressure was 200/130.

On admission to the hospital the patient appeared to be in a state of circulatory collapse. His temperature was 99.2° F., his pulse rate 104 per minute, and his respiratory rate 24 per minute; his blood pressure could not be measured. He preferred to lie on the right side. The fundi showed arteriosclerotic changes. The heart was enlarged; the sounds were very distant; there were no murmurs or friction rubs. The radial pulses were very feeble, but equal in volume, and the dorsalis pedis pulses could not be felt. The lungs were not demonstrably abnormal. Except for slight epigastric tenderness, the abdomen was negative.

The erythrocytes numbered 4,730,000 per cubic millimeter, the leucocytes 17,000. The hemoglobin content of the blood was 14.4 gm. per 100 c.c. The differential leucocyte count revealed 74 per cent neutrophiles, 20 per cent lymphocytes, and 6 per cent monocytes. The urine contained albumin (2-plus), 10 to 15 leucocytes per high-power field, and a few hyaline casts. The Kahn test on the blood serum was negative. The blood urea nitrogen was 50 mg. per cent. No roentgenograms were made. Electrocardiograms were taken on each of the three days the patient was on the ward (Fig. 1). Chief interest centered upon the T-wave and S-T segments in Leads II and III. In Lead II the T-wave was upright at the time of admission, and the S-T junction was isoelectric. On the second day the S-T junction was elevated 1 mm., and on the third day, 2 mm. The T-wave in Lead II became inverted on the third day. In Lead III the T-wave was upright and the S-T junction isoelectric at the time of admission. On the second day the S-T complex was of the "coronary" type, with suggestive "cove-plane" appearance, and the T-wave was inverted. On the third day, the T-wave was still deeper in Lead III. There was a persistent Q-wave in Lead III that measured approximately 33 per cent of the highest R-wave.

Because of the character of the pain, the history of hypertension, and the syncope, an initial diagnosis of dissecting aneurysm was made by two observers; others favored a diagnosis of myocardial infarction. Following supportive treatment the patient improved considerably, so that by the second day after admission his blood pressure had risen to 150/120. No cardiac murmurs or friction rubs were heard. There were no signs of fluid in the pericardium. On the third day after admission, the patient sat up in bed, beckoned to an orderly across the ward, and fell over dead.

The post-mortem diagnoses were dissecting aneurysm of the ascending aorta with rupture into the pericardium; slight aortic and coronary atherosclerosis; and chronic passive congestion of the liver and lungs. The pericardial sac was distended by 950 c.c. of blood. The right pleural cavity contained 300 c.c. of blood-tinged fluid, and the left 175 c.c. The source of the blood in the pericardial sac was found to be a rent 7 mm. in length in the outer coats of the right lateral aspect of the ascending aorta, 5 cm. above the base of the left ventricle and below the point of reflection of the pericardium. The rent communicated with a large space within the

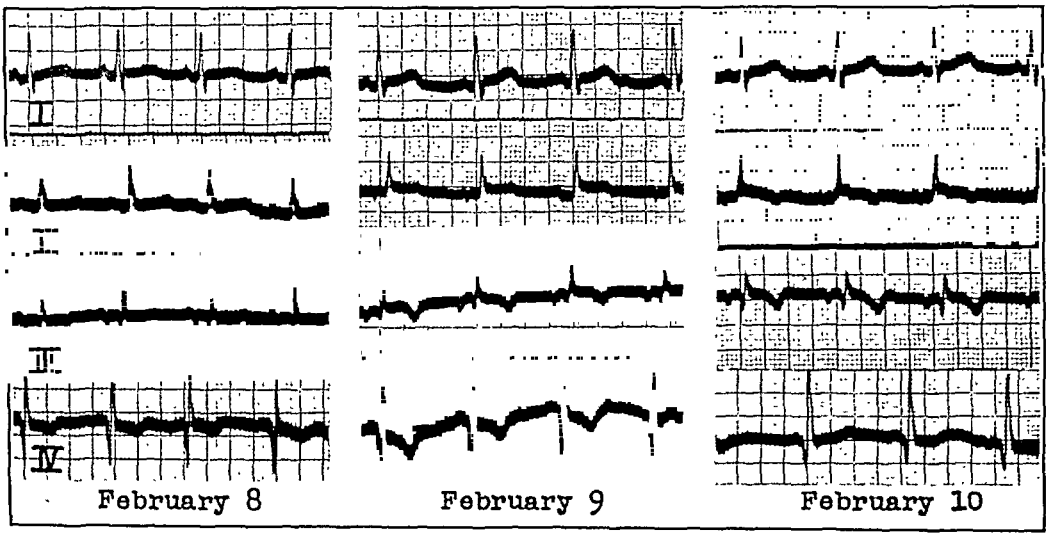

Fig. 1.—Serial electrocardiograms in Case 2.

wall of the ascending aorta. This space extended upward to within 1.5 cm. of the mouth of the innominate artery and downward behind the aortic valve. It was filled with clots of blood that separated the outer from the inner layer of the media of the vessel. Blood had invaded the subepicardial tissues and was present in the subepicardial layer of fat in the region of the aortic ring. Blood had also invaded the myocardium in this region, and completely surrounded the right coronary artery at a point about 1 cm. below its origin. The intima of the aorta was the seat of mild atherosclerosis, but there was no tear through this coat and careful search failed to reveal any connection between the aorta and the aneurysmal cavity. There was no evidence of syphilis. The heart valves were normal. The intima of the coronary arteries showed changes indicative of slight atherosclerosis. The heart was normal except for the portion invaded by blood. There was no gross or microscopic evidence of infarction. There was chronic passive congestion of the liver and lungs.

Comment.—The electrocardiograms in this case deserve comment because they simulated those of acute coronary occlusion (Fig. 1). The

progressive elevation of the S-T segment and inversion of the T-wave in Leads II and III are ordinarily considered characteristic of myocardial infarction involving the posterior and basal portions of the heart. These areas are supplied by the right coronary artery, which was the vessel involved by the dissection in this case. The progressive increase in depth of the Q-wave in Lead III is also evidence of a changing myocardial process. Even more striking "coronary" changes were reported by Elliot and Evans[14] in a case of ruptured abdominal aneurysm, and by Osgood, Gourley, and Baker[11] in a case of dissecting aneurysm in which no myocardial infarct was found. In Elliot and Evans's case, though no infarct was found, the coronary arteries were definitely narrowed. Their explanation was that in the presence of already narrowed coronary arteries the diminished blood flow associated with vasomotor collapse may have created sufficient anoxemia of the myocardium to bring about the changes in the electrocardiogram. Glendy, Castleman, and White[13] describe a case with "slight T-wave changes in Leads II and III, suggestive of cardiac infarction of the posterior or diaphragmatic type." They found that the aortic dissection involved the opening of the right coronary orifice. McGeachy and Paullin[7] reported a case of dissecting aneurysm with hemopericardium in which there were progressive T-wave changes, namely, inversion of a previously upright T-wave in Leads I and II.

In our patient, gross and microscopic studies failed to reveal evidence of coronary disease or of myocardial infarction. However, in the myocardium there was an ecchymosis which completely surrounded the right coronary artery and extended 1.5 cm. down the arterial trunk on all sides. It has been shown experimentally in dogs that electrocardiographic evidence of acute myocardial ischemia, characterized by distortion of the T-wave and elevation or depression of the S-T segment, frequently begins to manifest itself in Leads I, II, III, or IV after the cross section of a major coronary artery has been reduced by approximately 30 to 50 per cent.[15] Moreover, such hearts may show no evidence of myocardial infarction after periods of partial occlusion lasting one to two months. It seems reasonable to conclude, therefore, that in this case partial occlusion of the right coronary artery was probably effected during life by the blood which, at autopsy, was found to surround the vessel.

It may be argued that the electrocardiographic changes were the result of the hemopericardium. It is difficult to explain, on this basis, changes in the electrocardiogram that made their appearance one to two days previous to the patient's death, since the size of the tear in the aorta would suggest that leakage into the pericardium took place rapidly, causing a quickly fatal cardiac tamponade. That such was the case is borne out by the clinical course, for the patient presented no evidence of pericardial effusion up to the time of his sudden death.

At autopsy there was no connection between the ecchymosis about the coronary vessel and the tear responsible for the hemopericardium. Moreover, the elevation of the S-T segment was restricted mainly to Leads II and III, indicating a localized process, whereas, according to Schwab and Herrmann,[16] the S-T segment elevation seen in pericardial effusion ordinarily takes place in all three conventional leads and is the result of generalized myocardial ischemia. It is unlikely, therefore, that the hemopericardium was responsible for the electrocardiographic changes.

CASE 3.—C. G. H. 67451. The patient was a 55-year-old motorman, who was admitted to the neurologic service January 22, 1937, complaining of a "stroke." He had been standing about the carbarn when suddenly, without any warning, he fainted and fell to the ground. He was brought to the hospital in a stuporous condition. Later he stated that a moment before fainting he had a feeling that someone was drawing a rope tightly around his chest. However, he did not complain of pain at any time. Eight years previously he had been examined by a physician who told him his blood pressure was 265. There was no history of angina pectoris or of other cardiorespiratory symptoms.

On examination the temperature was 98° F., the pulse rate 52 per minute, and the respiratory rate 16 per minute. The blood pressure in the right arm was 68/60 and in the left arm 115/70. The patient was semistuporous but could answer questions slowly. The heart did not appear enlarged to percussion, but the retromanubrial dullness was increased. The heart sounds were very distant, and there was a systolic murmur at the base. The pulse in the right radial artery was imperceptible, but that in the left was easily felt. The lungs and abdomen were negative. The patient presented signs of left-sided hemiparesis. A diagnosis of cerebral hemorrhage was made, and the possibility of a syphilitic aortic aneurysm was entertained.

The erythrocytes numbered 3,100,000 per cubic millimeter, and the leucocytes 19,000. The hemoglobin content of the blood was 13 gm. per 100 c.c. The differential leucocyte count showed 92 per cent neutrophiles, 4 per cent lymphocytes, and 4 per cent monocytes. Examination of the urine revealed a moderate amount of albumin (1-plus), a few leucocytes, and numerous hyaline casts. The Kahn test on the blood serum was negative. The cerebrospinal fluid pressure was 250 mm. of water; the fluid was pink, contained 6,000 erythrocytes per cubic millimeter, and gave a negative Wassermann reaction. No roentgenograms or electrocardiograms were made.

There was no change in the patient's condition until thirty-three hours after admission, when he suddenly waved his arms about and fell over dead.

The post-mortem diagnoses were dissecting aneurysm of the aorta with rupture into the pericardial sac; marked cerebral atherosclerosis with recent infarction of the right lenticular nucleus; cardiac dilatation and hypertrophy; chronic passive congestion of the liver, lungs, and kidneys; and aortic and coronary atherosclerosis. The pericardial sac was distended by 250 c.c. of blood, much of which had clotted. The heart weighed 700 gm. Both sides of the heart were dilated, and the left ventricle was hypertrophied as well. The heart valves appeared normal. The coronary arteries were the seat of moderate atherosclerotic changes. Arteriosclerotic plaques were noted along the intima of the aorta. A transverse tear in the intima of the aorta, 2.5 cm. long and 2 mm. wide, was noted about 4 cm. above the aortic valve. This tear communicated with a cavity between the media and adventitia which extended from the level of the attachment of the aortic valve along the entire length of the aorta to the origin of the common iliac vessels. The lumen of the cavity was partially filled with blood clots, some relatively old and others

of more recent origin. Investigation of the great vessels arising from the arch of the aorta was not carried out at autopsy. There was passive congestion of the lungs, liver, and spleen. The liver was infiltrated with fat. There was a fresh area of softening in the right lenticular nucleus, surrounded by an area of edema partly involving the internal capsule.

Comment.—This patient is one of two (Cases 3 and 6) in this series in whom the presenting clinical manifestation was that of hemiplegia, a not unusual finding in dissecting aneurysm. Of significance, also, is the fact that the patient did not complain of pain. The most striking feature of the onset of the illness was the occurrence of syncope, preceded by a feeling of tightness in the chest.

CASE 4.—C. G. H. 67006. This patient was an unemployed white man, 70 years of age, who was brought to the hospital Jan. 11, 1937, in a semicomatose condition, unable to give a history. After his death, the following facts were obtained from his landlady. The patient had been in fair health until several weeks before he was admitted to the hospital. For about four weeks before admission he had suffered from epigastric pain of unknown nature, and anorexia, but his ordinary activities had not been curtailed. Two days before admission, he was forced to go to bed, apparently because of weakness. During this time he did not complain of pain. On the day of admission he fainted after arising from his bed. When his landlady found him he was able to recognize her, was very weak, and unable to talk. The only fact obtainable in the past history was that the patient had been discharged from a tuberculosis sanatorium twenty-two years previously.

On admission the patient appeared dehydrated. The skin was pale, cyanotic, and cold. The temperature was 95° F., the pulse rate 84 per minute, and the respiratory rate 26 per minute. The blood pressure was 96/70. Ophthalmoscopic examination showed blurred disk margins, compression of veins by arteries, flame-shaped hemorrhages, and old exudate. Dullness and numerous râles were detected over the upper anterior region of the left chest. The location of the heart borders could not be determined by percussion, but the heart sounds were of normal intensity and quality. A rough systolic murmur was heard over most of the precordium. The radial and dorsalis pedis pulses were readily palpable and equal in volume. The abdomen was negative.

The erythrocytes numbered 4,200,000 per cubic millimeter, the leucocytes 20,750. The hemoglobin content of the blood was 10 gm. per 100 c.c. The differential leucocyte count revealed 85 per cent neutrophiles, 1 per cent eosinophiles, 10 per cent lymphocytes and 4 per cent monocytes. The urine contained a trace of albumin and a great deal of sugar (4-plus). Tests for acetone and diacetic acid were negative. The urinary sediment contained 50 leucocytes per high-power field, 2 erythrocytes per high-power field, and an occasional hyaline cast. The Kahn reaction on the blood serum was negative. The cerebrospinal fluid pressure was 180 mm. of water. The fluid was clear and contained only 4 lymphocytes per cubic millimeter, but the Pandy reaction was positive (2-plus). The blood sugar was 363 mg. per cent, the carbon dioxide combining power, 33 volumes per cent; and the blood urea nitrogen, 15 mg. per cent. Two electrocardiograms showed frequent auricular premature beats. The P-R interval varied from 0.16 to 0.24 sec. The T-wave was isoelectric in Lead I, and a small Q-wave was present in Lead III. No roentgenograms were obtained.

The patient was moribund on admission and died thirty-five hours later without regaining consciousness. The clinical diagnoses were coronary occlusion, diabetes mellitus, and fibroid pulmonary tuberculosis.

The post-mortem diagnoses were dissecting aneurysm of the aorta with rupture into the left pleural cavity; arrested apical fibroid tuberculosis; chronic passive congestion and edema of the lungs; severe generalized atherosclerosis; myocardial fibrosis and degeneration; and chronic passive congestion of the liver and spleen. The pericardial sac contained 50 c.c. of straw-colored fluid. The heart weighed 395 gm. The myocardium was diffusely fibrosed. The valves were normal. The coronary arteries were tortuous, sclerotic, and in some places calcified; their lumina were narrowed, but patent throughout. The aorta was moderately dilated and was the seat of extensive atherosclerosis. A tear through the intima which communicated with a space between the layers of the media was found in the descending portion of the aorta, 4 cm. below the arch. This cavity extended upward to a level about 3 cm. above the intimal tear and downward to the bifurcation of the abdominal aorta. Another tear, through the outer layer of the media and adventitia, connected the aneurysmal space with the left pleural cavity, which contained partly organized blood and about 500 c.c. of serosanguineous fluid. The lungs showed edema and chronic passive congestion. There were old fibrous tuberculous lesions at both lung apices. There was chronic passive congestion of the liver and spleen. The pancreas was normal.

Comment.—Because of the meager history in this case, the nature of the epigastric pain from which the patient suffered could not be ascertained. Apparently the pain was not severe enough to cause the patient to limit his activities or to seek medical advice. According to those in closest contact with the patient during the final illness, the outstanding complaint was weakness and, finally, syncope.

CASE 5.—C. G. H. 75763. The patient was a white male clerk 65 years of age, who was admitted to the hospital June 11, 1937, complaining of having "*passed out.*" He had just finished his noon meal that day when he became aware of a feeling of oppression beneath the lower sternum and numbness in the left arm down to and including the little and ring fingers. He had no pain, dyspnea, or cough. He soon became so weak that he fell to the floor and had to be brought to the hospital. The past history was irrelevant.

Physical examination revealed a well-developed thin man who was conscious but obviously in a state of circulatory collapse. The temperature was 95° F., the heart rate 90 per minute, and the respiratory rate 20 per minute. It was impossible to measure the blood pressure in either arm. The skin was cold, pale, and moist. The lips and fingertips were cyanotic. The pupils were equal, regular, and reacted to light and in accommodation. Examination of the fundi revealed arteriosclerotic changes in the vessels, but no retinal hemorrhages or exudate. The trachea was in the midline; there was no tracheal tug. The lungs were negative. Percussion showed that the heart was slightly enlarged to the left, and the apex beat was in the fifth interspace 10 cm. to the left of the midline. The heart sounds were very distant, and the heart was grossly irregular. No murmurs or friction rubs were heard. The peripheral pulses could not be felt. The abdomen was negative.

The erythrocytes numbered 3,700,000 per cubic millimeter, and the leucocytes 21,000. The hemoglobin content of the blood was 12 gm. per 100 c.c. The differential leucocyte count showed 80 per cent neutrophiles, 1 per cent eosinophiles, 18 per cent lymphocytes, and 1 per cent monocytes. The Kahn reaction on the blood serum was negative. The electrocardiogram showed nothing but numerous auricular and ventricular premature beats.

Following the intravenous administration of 700 c.c. of a 5 per cent glucose solution, the blood pressure was obtained at 50/30, and the patient seemed somewhat

improved. However, while talking to a nurse, he suddenly began to moan and toss about and within a few minutes was dead. Death occurred thirteen hours after the onset of symptoms. The clinical diagnosis was coronary thrombosis.

The post-mortem diagnoses were dissecting aneurysm of the aorta; moderately severe aortic and coronary atherosclerosis; cardiac hypertrophy; myocardial fibrosis and degeneration; and chronic passive congestion of the lungs. The autopsy was limited to the thorax. The pericardial sac contained 125 c.c. of blood and numerous blood clots. The heart was enlarged and, with the attached aorta, weighed 860 gm. The left ventricle was hypertrophied. The endocardium and valves were normal. The lumen of the anterior descending branch of the left coronary artery was narrowed by intimal atherosclerosis. The other coronary vessels showed slight sclerosis, but their lumina were not narrowed. In the intima of the aorta were numerous elevated yellow plaques, many of which were calcified. About 4 cm. above the level of the aortic valve was a linear, irregular, intimal tear, through which the lumen of the aorta communicated with a cavity which had formed between the outer layers of the media. This cavity, which was partially filled with fresh and organizing blood clots, extended from the level of the aortic valve to the bifurcation of the aorta. Near its cardiac end the dissecting aneurysm communicated directly with the pericardial sac. The blood had dissected upward along the innominate artery into the right subclavian and common carotid vessels, and also had progressed for a distance of 1.5 cm. along the posterior half of the left common carotid and left subclavian arteries. The dissection involved most of the intercostal vessels, as well as the abdominal branches of the aorta. The lungs were congested and edematous.

CASE 6.—C. G. H. 77601. This patient was a white housewife, 59 years of age, who was admitted to the hospital July 24, 1937, in a stuporous condition. According to her daughter, the patient had been in fairly good health until six days before admission, when during an automobile ride she suddenly felt faint and had to be taken home. Following this episode she did not seem ill except for slight difficulty in talking, and continued in good health for two days. At the end of this time generalized weakness forced her to go to bed; she gradually became drowsy but did not lose consciousness. She was able to move all her extremities, and at no time complained of pain. Since the age of seventeen years, her general health had been good except for frequent headaches. Six years previously, she had been told by a physician that her blood pressure was 300. At that time her ankles had been swollen, but aside from this fact there was no history of cardiorespiratory symptoms.

Physical examination revealed an elderly woman lying quietly in bed, stuporous, but not unconscious. The temperature was 99.6° F., the pulse rate 88 per minute, and the respiratory rate 20 per minute. The blood pressure was 220/110 in each arm. The retinal arteries were narrowed, and there were a few old retinal hemorrhages. The lungs were not demonstrably abnormal. The heart was enlarged, and a systolic murmur was heard at the apex. The abdomen was normal. Neurologic examination was unsatisfactory because of poor cooperation. There was evidence of motor aphasia, right-sided facial paresis, and weakness of the right arm and right leg. The abdominal reflexes were not obtained, but the tendon reflexes were normal; no abnormal plantar signs were elicited. A diagnosis of hypertension and thrombosis of the left lenticulostriate artery was made.

The erythrocytes numbered 3,570,000 per cubic millimeter, and the leucocytes 11,000. The hemoglobin content of the blood was 12.5 gm. per 100 c.c. The differential leucocyte count was normal. The urine contained albumin (3-plus) and a few hyaline casts. The Kahn reaction on the blood serum was negative. The cerebrospinal fluid was normal. No roentgenograms were made. The course of the patient's illness was uneventful for fifty-six hours, when she died suddenly.

The post-mortem diagnoses were dissecting aneurysm of the aorta, with hemopericardium; extensive generalized atherosclerosis; arterio- and arteriolonephrosclerosis; coronary sclerosis; myocardial fibrosis; cardiac hypertrophy, pulmonary congestion and edema; chronic cholecystitis and cholelithiasis; and chronic passive congestion of the liver. The pericardial sac was distended and contained 500 c.c. of blood. The heart was not weighed separately, but with the pericardium and thoracic aorta weighed 600 gm. The cardiac muscle was hypertrophied and fibrotic. The heart valves were normal. The coronary arteries were rigid and tortuous, but the lumina were patent. The aorta was dilated, and the intima lined with many atheromatous and calcified plaques. At a point 2.5 cm. above the aortic valve, on the posterior wall of the aorta, was a transverse intimal tear which communicated with a cavity between the medial and adventitial coats. On the exterior surface of the aorta, but on the anterior aspect, was another perforation, 2 mm. in diameter, which communicated with the pericardial cavity. The aneurysmal cavity surrounded the aorta completely from the beginning of the ascending aorta to the midportion of the thoracic aorta; but from this point down to, and including, the first portion of the celiac arteries, only one-half to three-quarters of the circumference of the vessel wall was involved. All the vessels arising from the arch of the aorta were extensively involved, and both common carotid arteries were dissected as high as their bifurcations. Throughout the course of both common carotid arteries the clot bulged into the lumina, causing marked reduction of their caliber. There was chronic passive congestion of the lungs and liver. The kidneys were small, contracted, and weighed 150 gm. The surfaces presented coarse and fine granulations, and the cortices were grossly distorted. There were no gross abnormalities of the gastrointestinal tract. The cerebral arteries were the seat of advanced atherosclerosis, leading to marked narrowing of the lumina. Except for a few old tiny areas of softening, the brain was not remarkable; there was no gross infarction.

DISCUSSION

In addition to the unusual manifestations presented by the first two cases, consideration of the character of the disease in the entire group of six cases which we have reported brings out several unusual features which deserve comment. The common conception of the onset of dissecting aneurysm is that of a sudden dramatic catastrophe which is ushered in by unbearable pain. In view of this conception, it is significant that only two of our patients suffered from severe pain and that three were apparently free from pain throughout their illness. Wood, Pendergrass and Ostrum[10] have previously called attention to the absence of pain in dissecting aneurysm. Most observers also state that the arterial pressure is typically high in dissecting aneurysm and that the presence of hypertension is an important sign in the differential diagnosis between this condition and myocardial infarction. In our cases, five of the six patients either had normal blood pressure or were in a state of peripheral circulatory collapse at the time of admission.

The outstanding symptom in all six cases was syncope or weakness. Four of the six patients herein reported fainted either at the onset of their illness or shortly thereafter, and the remaining two suffered from dizziness and weakness but did not actually lose consciousness. Though

we have no statistical information concerning the occurrence of syncope in coronary occlusion, it is certainly not a common initial symptom. On the other hand, fainting is quite common in dissecting aneurysm,[2, 3, 10] and is frequently the presenting symptom. In view of the difficulties of differentiating between coronary occlusion and dissecting aneurysm, this symptom, either in the presence or absence of pain, takes on considerable importance.

It is of interest that six cases of dissecting aneurysm were encountered within the short space of seven months, in view of the fact that in the preceding nine years only ten cases had come to necropsy at this hospital.[17]

SUMMARY

Six cases of dissecting aneurysm of the aorta, autopsied between January and July, 1937, are reported. In two cases the correct diagnosis was made during life.

One patient presented a conspicuous increase in the pulse volume of the left common carotid artery. Dissection along this vessel causing interference with the periarterial sympathetic plexus is proposed as the explanation of this sign.

One patient presented electrocardiographic changes characteristic of coronary occlusion, which apparently resulted from extravasation of blood about the right coronary artery.

Four patients lost consciousness at the onset, and all complained of dizziness or weakness. The importance of syncope in the differential diagnosis between dissecting aneurysm and coronary thrombosis is discussed.

Pain was not a prominent symptom in four of the six cases.

An elevated blood pressure at the time of admission was observed in only one case.

Intimal tears were observed in four cases.

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THE VECTORCARDIOGRAM*

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INTRODUCTION

WALLER, who was the first to obtain graphic records of the electric currents produced by the human heart, had a clear conception of the relation between the direction of the cardiac electromotive force and the relative potential of the various extremities. One of his early papers,[1] published in 1889, contains a diagram which shows the distribution of the isopotential surfaces within the trunk when the electrical axis of the heart has a base-apex direction. In 1913 Einthoven, Fahr, and de Waart[2] devised a method of computing the "manifest" magnitude and the direction of the resultant electromotive force produced by the heart at a given instant during the cardiac cycle. They made extensive use of this method in studying the influence of the respiratory changes in the position of the heart upon the form of the ventricular complex. In the same article they published an enlarged reconstruction of a normal electrocardiogram in which the QRS complexes of the three leads were arranged one above the other in their proper time relations so that simultaneous points fell on the same ordinate. This reconstruction enabled them to measure accurately the voltage recorded in each lead at ten successive instants equally spaced throughout the QRS interval, and thus to compute the corresponding value of E, the "manifest" magnitude of the cardiac electromotive force, and of α, the angle which defines its direction with respect to the horizontal. This method of analyzing the electrocardiogram was later employed by Williams,[3] and by Lewis,[4] who made important use of it in his studies of bundle branch block, of ventricular hypertrophy, and of auricular flutter.[5] Lewis laid great emphasis upon the rotation of the electrical axis because he believed that the changes in the direction of this axis gave direct evidence of similar and coincident changes in the direction in which the excitatory process as a whole was spreading over the cardiac muscle.

Since the resultant electromotive force produced by the heart at a given instant has both magnitude and direction, it may be represented by a vector drawn from the center of Einthoven's triangle as origin. When the excitatory process is advancing or retreating the size and direction of this vector vary from instant to instant so that its terminus describes a continuous curve. In mathematical language, this curve is a vector function of the time. In 1920 Mann,[6] utilizing data

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published by Einthoven and his associates as well as material of his own, constructed a number of curves of this kind and called them monocardiograms. Granting the priority of this name, we prefer to call them vectorcardiograms in order to emphasize the true nature of the difference, in a mathematical sense, between them and ordinary electrocardiographic curves, which are scalar functions of the time. In 1931 Mann[7] published a second article on this subject in which he stated that he had constructed an apparatus which made it possible to record the monocardiogram directly. We understand that this apparatus was demonstrated on one or more occasions, but it has not been described in the literature and no curves taken with it have been published.

A few years ago we became interested in the possibility of using the cathode-ray oscillograph for this purpose. Having found this feasible, we have constructed the necessary apparatus and have taken a considerable number of entirely satisfactory curves. The methods employed were described and sample curves of various types were shown at a meeting of the American Society for Clinical Investigation, in May, 1937.[8] At that time we were not aware of any work along this line other than the studies already mentioned. In August, 1937, however, Hollmann and Hollmann[9] described a somewhat different method of using the cathode-ray oscillograph to record the vectorcardiogram and called attention to Schellong's work,[10] which was presented at a medical meeting in Germany in April, 1936. Thus, as often happens, technical improvements, in this instance in the design of the cathode-ray tube, led to the independent development of similar methods in several places at about the same time.

METHODS

In principle the method we have employed is exceedingly simple. The inner surface of the larger end of the cathode-ray tube is coated with fluorescent material. Where the beam of electrons generated by the tube strikes this screen a brilliant luminous spot is produced. By varying the voltages on the different electrodes, the beam of electrons may be focused, the velocity of the electrons constituting the beam may be varied, and the beam current may be controlled. The tube is provided with two sets of deflecting plates; a difference in potential between the plates of the first set shifts the beam, and hence the luminous spot, in the vertical direction, and a difference in potential between the plates of the second set shifts the beam in the horizontal direction. Within wide limits the displacement of the beam in either direction is strictly proportional to the voltage applied to the corresponding set of plates. The displacement takes place practically instantaneously when the voltage is applied, and no overshooting occurs. The sensitivity of the cathode-ray tubes we have used is such that about twenty-five volts are required to move the luminous spot through a distance of 1 cm. In order, therefore, to obtain satisfactory vectorcardiograms the voltages obtained from the electrodes on the extremities must be amplified at least 25,000 times, and much greater amplification is desirable.

The connections between the body and the deflecting plates of the cathode-ray tube are arranged as indicated in Fig. 1. The right-arm and left-arm electrodes are connected through a suitable amplifier to the deflecting plates which shift the

spot in the horizontal direction, or along the x axis. The polarity is so arranged that relative negativity of the right-arm electrode displaces the spot to the right, and relative positivity of this electrode displaces it to the left. The gain-control of the amplifier is adjusted until the spot moves 1, 2, or 3 cm. when one millivolt is introduced into the input circuit. The spot then moves back and forth along the x axis in step with the difference in potential between the two arms, and, if its movements are photographed on a film moving at a uniform speed, standard Lead I is faithfully recorded.

Einthoven and his associates showed that if the magnitude of the cardiac electromotive force is represented by E and the angle which defines the direction of this force with respect to the x axis by α, the deflection in Lead I is equal to $E \cos \alpha$. This is the horizontal component of the cardiac vector, and it is obtained as described in the preceding paragraph. In order to obtain the vertical component, we make use of a simple network. The three extremity electrodes employed in taking

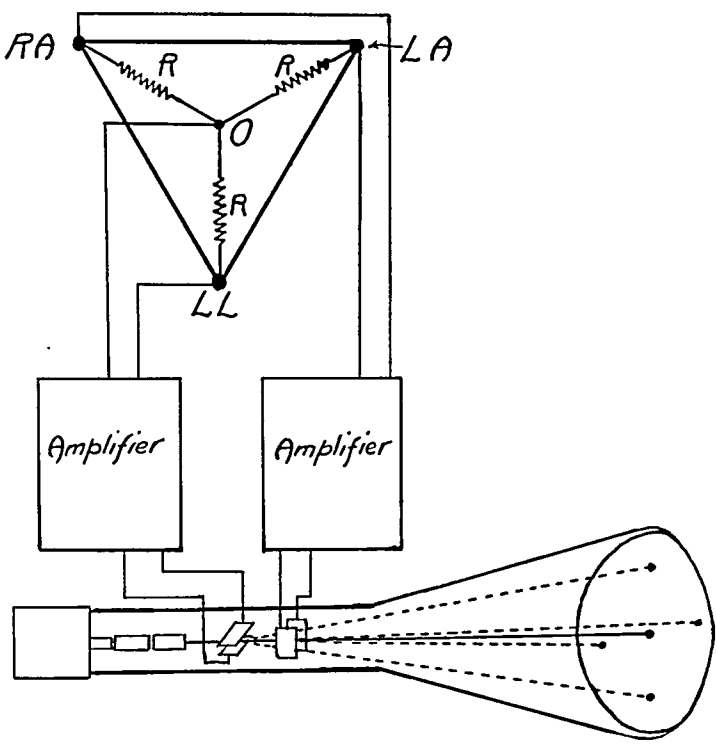

Fig. 1.

the standard limb leads are connected through equal resistances of 5,000 or more ohms to a central terminal. In previous communications[11, 12] it has been shown that, when this is done, the difference in potential between the central terminal and the left-leg electrode must always be equal to one-third the sum of the potential differences recorded by Leads II and III. It has also been shown that one-third of the sum of these potential differences is equal to $E \sin \alpha$, the vertical component of the cardiac vector, divided by $\sqrt{3}$. In order to place this component upon the Y axis of the cathode-ray tube, the central terminal and the left-leg electrode are connected to the second set of deflecting plates by way of a second amplifier adjusted to give a deflection 1.7* times as great as the first for the same input. The connections are so made that relative negativity of the central terminal produces a downward, and relative negativity of the left-leg electrode an upward, deflection.

*$\sqrt{3} = 1.73 +$

When these arrangements have been completed, the cardiac electromotive force displaces the luminous spot on the screen of the tube through a horizontal distance proportional to $E \cos \alpha$ and through a vertical distance proportional to $E \sin \alpha$. Consequently, this spot always marks the terminus of the cardiac vector, and, as this vector varies in magnitude and direction, it moves along a continuous curve until the cardiac electromotive force becomes zero, when it returns to its isoelectric position at the center of the screen. This curve may be photographed with a camera of the ordinary type by opening the shutter just long enough to record a single heartbeat. Time is measured along the curve. It may be recorded by placing an alternating voltage of the desired frequency upon the grid of the tube. When this is done, the continuous curve is broken into segments each of which represents a known interval of time.

This method has several important advantages over others which might have been employed to the same end. One of its chief advantages is that most of the equipment is of a standard type and may be used for many purposes other than the study of the vectorcardiogram. This equipment consists of a commercial cathode-ray oscillograph of the kind which is supplied with a separate terminal for each of the four deflecting plates, two amplifiers which will give sufficient voltage amplification without distortion of the electrocardiographic deflections, a device by means of which a standardizing voltage of 1 mv. may be introduced into the input circuit of either amplifier, and resistors for the network described, which may also be used to advantage in taking precordial and esophageal leads. We have used a 5 in. tube with a time delay screen which gives a brilliant spot and a pronounced afterglow, which makes it possible to see the path followed by the spot for several seconds. Tubes of the high vacuum type seem to give better definition than those of the low vacuum type. The two amplifiers which we have used are of different kinds. One is a three-stage push-pull direct current amplifier which gives a voltage gain of 25 to 30 thousand. The second is a three-stage push-pull amplifier with resistance-condenser coupling between the stages. This amplifier will give a voltage amplification of 100,000 or more and has an over-all time-constant of nearly 3 seconds, so that distortion of the slower electrocardiographic deflections is negligible. We hope to improve our technique by replacing the direct current amplifier with a second amplifier of this type, which will make it possible to use greater amplification when the voltage of the electrocardiographic deflections is small, and to obtain more satisfactory vector diagrams of the P and T deflections.

RELATIONS BETWEEN THE VECTORCARDIOGRAM AND THE STANDARD LEADS

The diagram shown in Fig. 2 illustrates the relations between the vectorcardiogram and the standard limb leads. In this diagram the center of Einthoven's equilateral triangle coincides with the isoelectric point of the curve enclosed by it, and the projections of this point upon the sides of the triangle coincide with the isoelectric levels of the three leads. These leads are shown in their proper orientation and the points on the curve which correspond to their chief peaks are indicated.

It will be noted that Leads II and III are inverted. It would, of course, be possible to avoid this by reversing the polarity of the vertical component of the cardiac vector, but this cannot be done without violating the convention established by Einthoven, who represented the heart's electromotive force by an arrow pointing in the minus-plus direction or from the active toward the resting muscle. This convention has been

universally accepted, and it should not now be abandoned. The potential value of the vectorcardiogram depends upon the possibility of obtaining from it information regarding the spread and retreat of the excitatory process which cannot be obtained from the standard limb leads without the expenditure of an excessive amount of time and labor. This information will be obtained more easily if the customary method of representing the orientation of the electrical axis or cardiac vector is followed.

OBSERVATIONS

The vectorcardiogram of a normal subject is shown in Fig. 3. The movements of the spot which represent the P- and T-waves are very

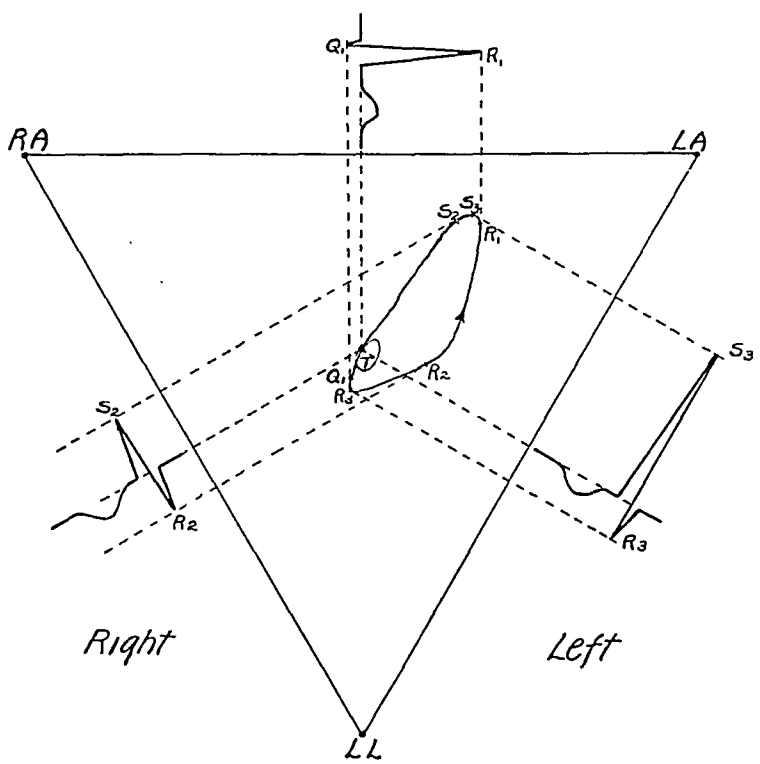

Fig. 2.

small and their details are lost in the uniformly black area which surrounds the isoelectric point. The large closed loop represents the QRS complex. At the time when the photographs were taken, it was noted that the luminous spot traversed this loop in the clockwise direction. In other words an observer who followed the path of the spot would find the enclosed area constantly on his right. Following the usual mathematical convention, we shall speak of the areas enclosed by loops of this kind and of the loops themselves as negative; whereas, when the motion of the spot was counterclockwise, we shall refer to the loop inscribed as positive. The observation made with reference to the direction of motion of the spot is confirmed by comparison of the vectorcardiogram and the standard leads which are also reproduced. Since there

is a definite S deflection in Lead I, the terminal part of the loop must lie to the right of the isoelectric point. A good idea of the velocity of the spot in various parts of its course may be gained from the curves obtained when the grid potential, which controls the beam current of the cathode-ray tube, was made to oscillate 100, 200 or 1,000 times per second. These curves show that the QRS interval was about 0.07 or 0.08 second, and that the spot moved much faster during the earlier than during the later portions of this period.

It should be mentioned that the apparatus used in taking the vectorcardiogram was adjusted to give a horizontal displacement of 10 mm. and a vertical displacement of 17 mm. when a millivolt was impressed upon the input circuits of both amplifiers. After this adjustment had

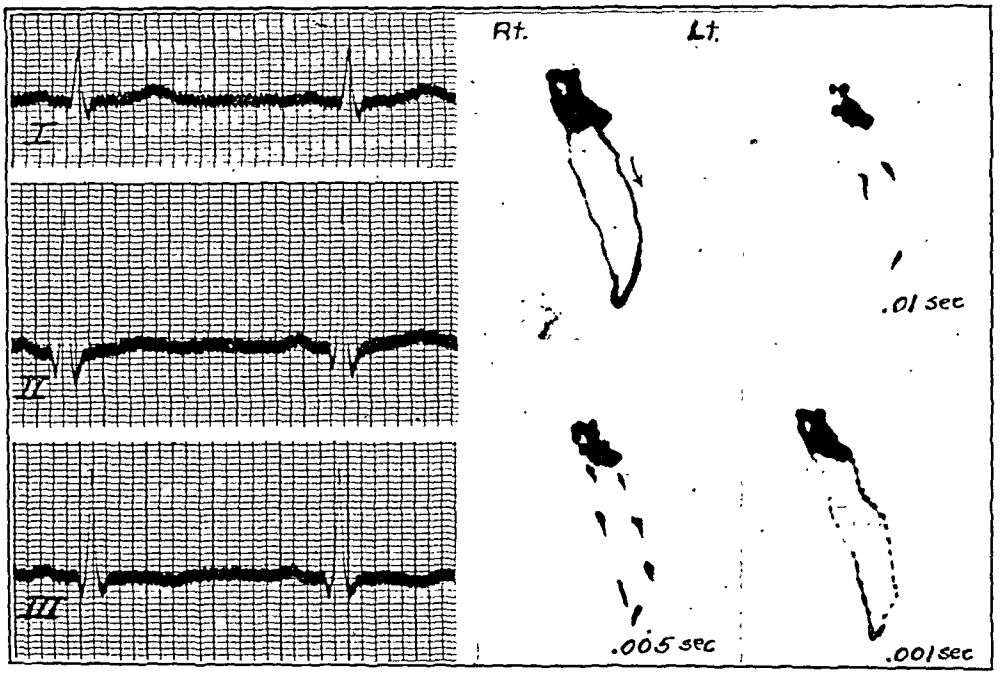

Fig. 3.

been made the accelerating voltage of the cathode-ray tube was frequently reduced in order to obtain larger curves. Measurements of the vectorcardiograms reproduced in this article cannot, therefore, be expressed in millivolts except by comparison of the dimensions of these curves with the voltages of the deflections of the standard leads.

Some years ago Lewis reported that left ventricular preponderance and the common type of bundle branch block were both characterized by an almost uniform counterclockwise rotation of the electrical axis during the QRS interval.* In right ventricular preponderance and bundle branch block of the rare type, on the other hand, clockwise rotation of the electrical axis was found to occur. Lewis based his conclu-

*In the case of bundle branch block only those deflections written during the first half of this interval were analyzed.

sions upon the analysis of a relatively small number of electrocardiograms, and we hope to extend his observations. For the present we shall merely indicate how the vectorcardiogram may be used for this purpose by describing a few curves obtained from cases of the kind which he studied.

A good example of vectorcardiograms obtained when the standard leads show left axis deviation is shown in Fig. 4. In this instance the QRS interval is 0.11 or 0.12 second. It is possible that a defect in intraventricular conduction was present, but the QRS loop shows none of the peculiarities in contour which that condition often produces. This loop is of the positive variety. Throughout the greater part of the QRS interval the cardiac vector rotated counterclockwise. Near the end of this interval its magnitude gradually decreased, but its direction re-

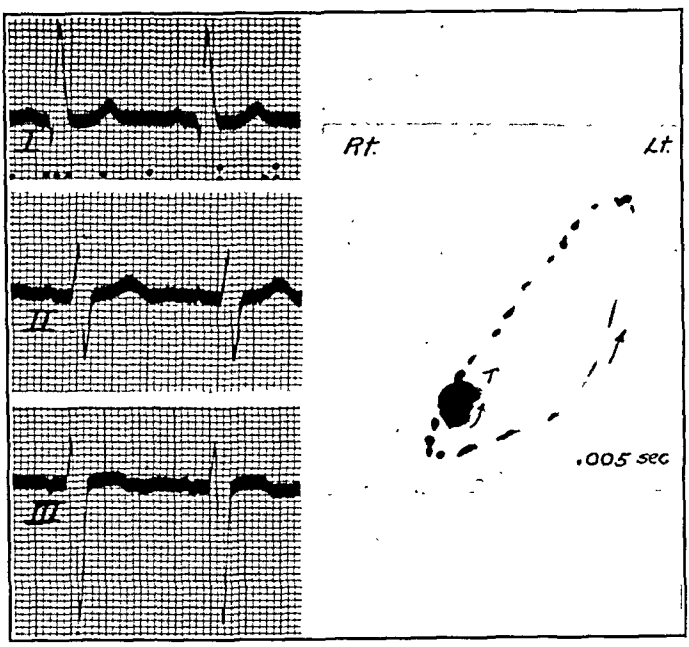

Fig. 4.

mained nearly constant. At –50° this vector attained its greatest length. The T-loop is also positive. The cardiac vector rotated counterclockwise during its inscription. The inclination of the longest vector of this loop cannot be determined accurately, but it is obvious that it is separated from the maximal QRS vector by an angle of considerably less than 180°.

A second example of left axis deviation is shown in Fig. 5. Here the maximal QRS vector lies between –15° and –20° and the greatest T vector points in the opposite direction. The QRS interval is well within normal limits. The larger of the two areas enclosed by the QRS loop is positive; the smaller, which is near the isoelectric point, is negative. The cardiac vector did not rotate through a very wide angle, but such rotation as occurred was mainly counterclockwise.

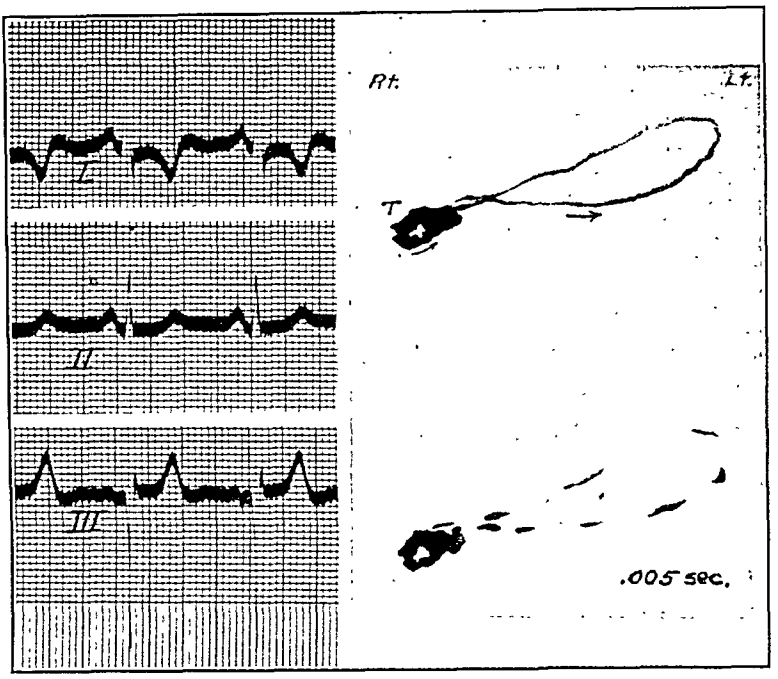

Fig. 5.

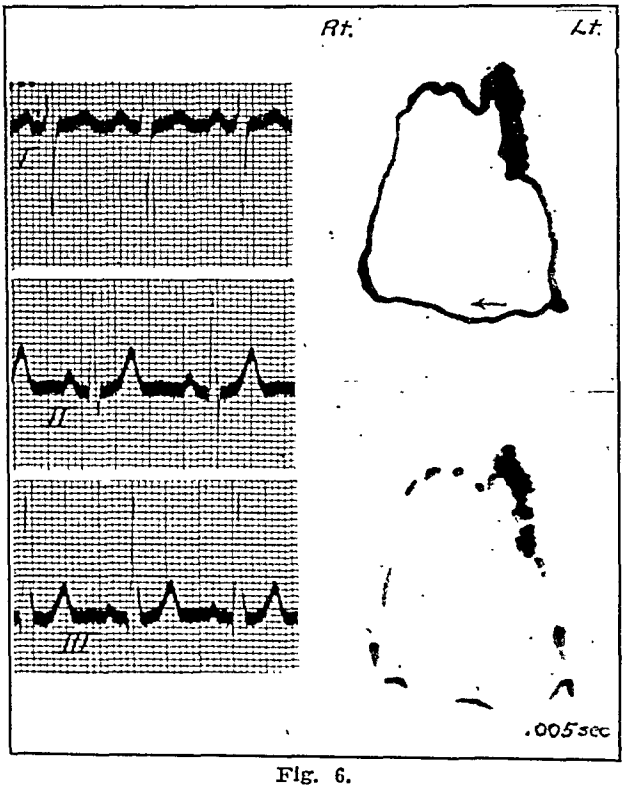

Fig. 6.

The vectorcardiogram obtained in a case of right axis deviation is shown in Fig. 6. The QRS interval is approximately 0.08 second. The area enclosed by the QRS loop is negative and very large. During the inscription of this loop the rotation of the cardiac vector was mainly clockwise, but at the beginning of the QRS interval and again at the end a temporary reversal in the direction of its rotation took place. It should be noted that it is necessary to distinguish between the direction taken by the spot during the inscription of the QRS loop and the direction in which the electrical axis rotates during the same period. If the luminous spot continues to move in the same general direction it may execute an S-shaped curve, such as occurs near the isoelectric point in

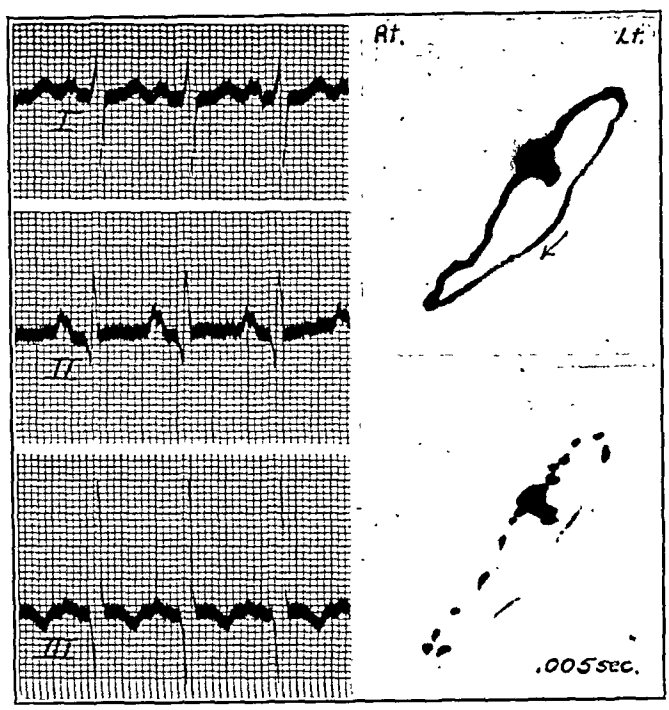

Fig. 7.

the present instance. During a period of this kind the electrical axis swings first one way and then the other, but turns through a relatively small angle. The cardiac vector reached its maximum length when its inclination was +120°. It was, however, already near its maximum magnitude when at +75°. During the inscription of T the amount of rotation was very slight.

A second example of right axis deviation is shown in Fig. 7. Here again the area enclosed by the QRS loop is negative, but it is relatively small. The cardiac vector rotated clockwise through an angle of approximately +180°. During the first part of the QRS interval its inclination was about −50°; during the last part and at the time when it reached its greatest length its inclination was about +125°. The T

loop is very small and cannot be made out clearly. The R_1 and Q_3 peaks were nearly synchronous, as were also the S_1 and R_3 peaks.

In bundle branch block the vectorcardiogram is often very bizarre in outline. Both the rotation of the cardiac vector and its changes in magnitude may be strikingly irregular. Beading of the curve, and accessory loops are common.

An example of left bundle branch block is shown in Fig. 8. The main QRS loop is positive, but the small accessory loop at about –30° is negative and is conspicuously beaded. There is also a beaded projection in the neighborhood of –60°. These irregularities correspond to the deep notches which deform the QRS complex of the standard leads.

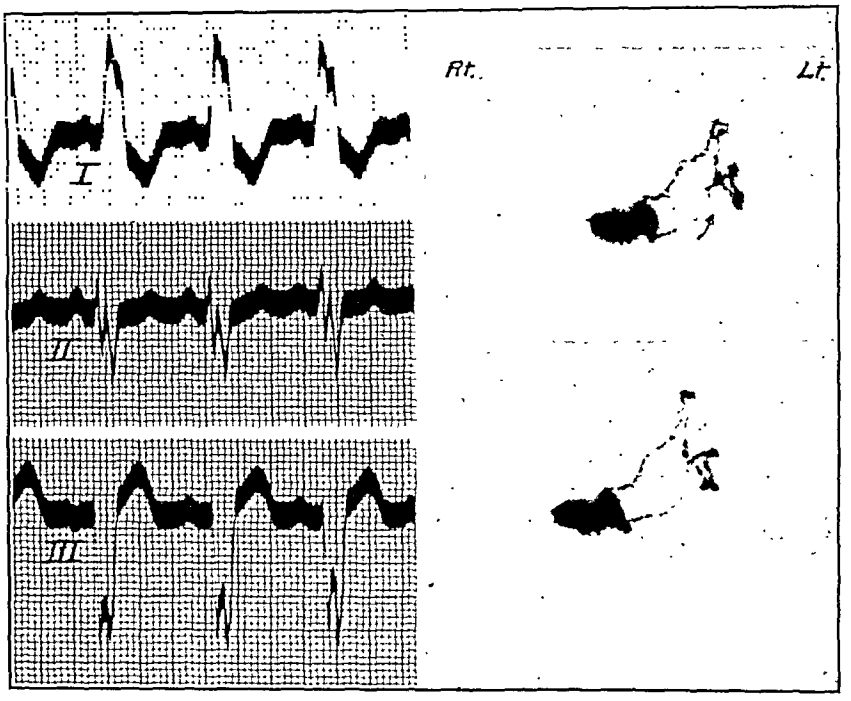

Fig. 8.

Beads occur when for a short period the magnitude and direction of the cardiac vector remain nearly constant. Loops are produced when the cardiac vector temporarily reverses the direction of its rotation, and at the same time undergoes a transient reduction or increase in magnitude.

The left bundle branch block curve shown in Fig. 9 is of a different form. The cardiac vector rotated counterclockwise through a relatively small angle. It reached its greatest length when its inclination was –60°. There is considerable beading of the QRS loop, but there are no accessory loops and the QRS complexes of the standard leads are not conspicuously notched. The direction of the maximal T vector is almost exactly opposite to that of the maximal QRS vector.

A curve which depicts an interesting example of right bundle branch block is shown in Fig. 10. During the inscription of the QRS loop the rotation of the cardiac vector was counterclockwise, but during

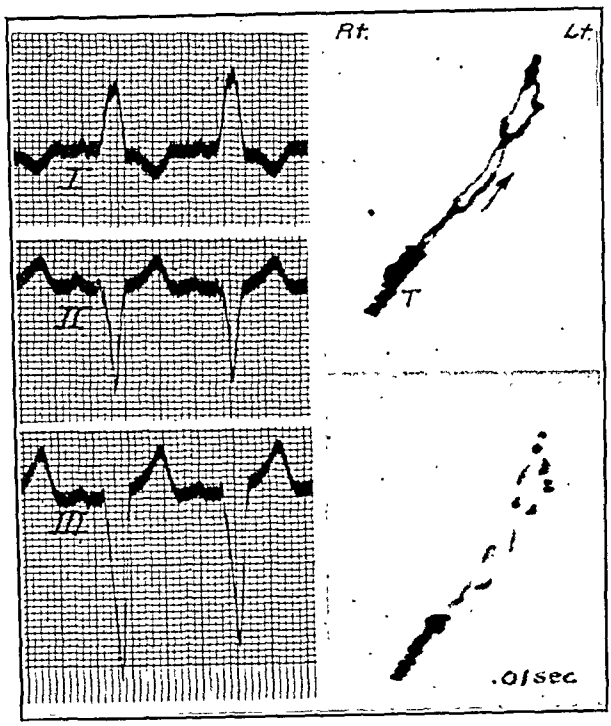

Fig. 9.

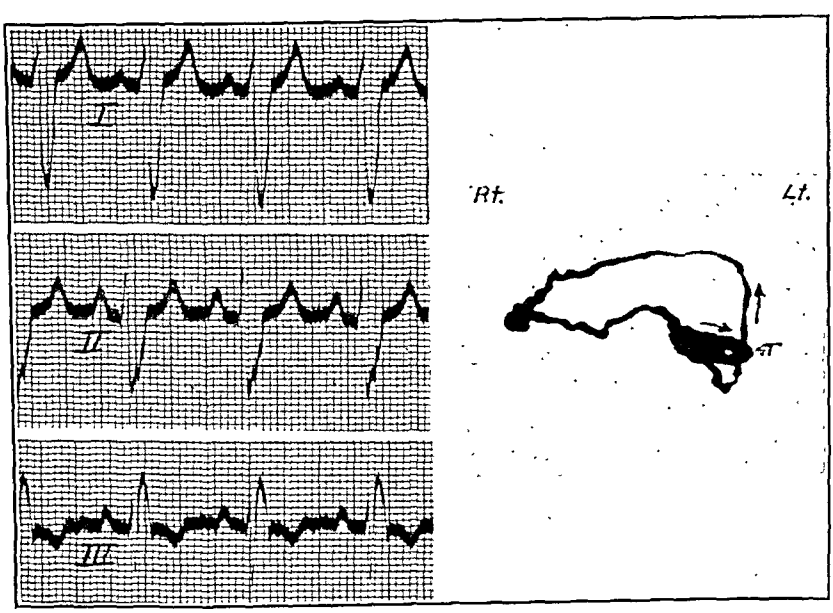

Fig. 10.

the inscription of the T loop it was clockwise. There is considerable beading of the QRS loop, but it is confined largely to the region of the tip inscribed at the time when the magnitude of the vector was maximal

and its inclination approximately –170°. The patient was a young man who presented typical signs of Fallot's tetralogy.

Another somewhat unusual case of right bundle branch block is illustrated in Fig. 11. The main QRS loop is positive; the beaded acces-

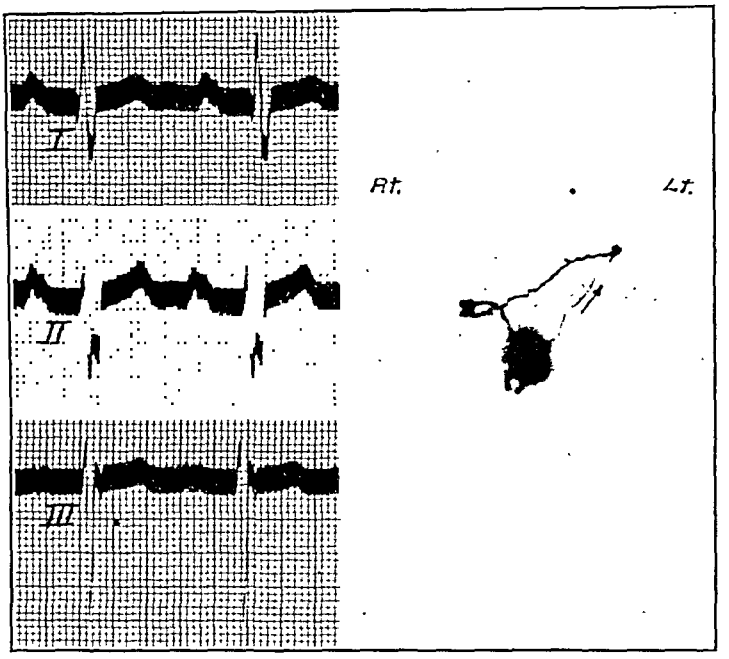

Fig. 11.

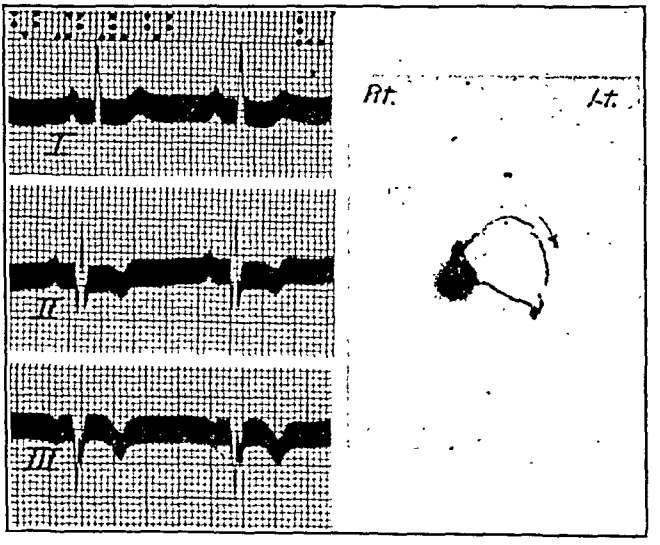

Fig. 12.

sory loop which corresponds to the deep notch seen in the QRS complex of Lead II is negative. The inclination of the largest QRS vector is approximately –60°, as in some cases of left bundle branch block. The patient was a young woman with congenital heart disease. Autopsy disclosed the presence of a huge ostium primum in the auricular septum.

Evidently, the cardiac vector may rotate counterclockwise in right bundle branch block as well as in left.

Fig. 12 illustrates the appearance of the vectorcardiogram in a case of infarction of the diaphragmatic wall of the heart. During the first part of the QRS interval, and also during the last part, the cardiac vector pointed almost straight upward. During the remainder of this interval it rotated clockwise and inscribed a loop which closely resembles the outline of a leaf. At the time when it attained its greatest length its inclination was about +30°.

COMMENTS

Our limited experience with the vectorcardiogram does not warrant any conclusion as to its ultimate usefulness. Nevertheless, it may be worthwhile to point out some of the ways in which it may possibly be utilized to advantage in teaching, in cardiac diagnosis, and in research.

In teaching it should prove helpful in the presentation of a variety of subjects. In this field it possesses advantages similar to those offered by vector methods in physics and mechanics. It makes it possible to visualize the electromotive force of the heart as a single natural entity unobscured by the artificiality and the complexities introduced by splitting it into a system of components in the arbitrary frame of reference defined by the standard leads. The importance of this difference will be easily appreciated if the vectorcardiogram is used to study the effects produced by the rotation of the heart which takes place on deep inspiration. Instead of the complicated changes which take place in the form of the ventricular complexes of the three leads one sees a simple clockwise rotation of the whole curve accompanied by very minor changes in its form due to twisting of the heart on its long axis. The vectorcardiogram can hardly fail to make it easier for the student to grasp the relations between the three standard limb leads, the reason why homonymous peaks in the different leads are frequently asynchronous, the meaning of axis deviation, and the manner in which notching of the QRS complex depends upon irregularities in the growth and decline and in the changes in direction of the cardiac electromotive force.

It is more difficult to foresee what advantages the vectorcardiogram may bring to the field of cardiac diagnosis. It is unlikely that it can offer important help in the identification of the arrhythmias, or in the measurement of the P-R, QRS, and Q-T intervals. It is possible, on the other hand, that it may aid in the detection and the differentiation of abnormalities in the form of the ventricular complex. It is true that by expending a great deal of time and effort one may derive the vectorcardiogram from the standard electrocardiogram, or vice versa, and that the two are in this sense equivalent. It is likewise true that mere inspection of the standard electrocardiogram will often enable one

to predict the general contour of its vector counterpart and to infer the general direction of rotation of the cardiac vector and its approximate inclination at the time when it reaches its greatest length. This is not possible in all instances, and there must be many in which the vectorcardiogram will furnish data which could not be obtained from the standard leads without excessive labor, if at all. In future studies we hope to determine whether the vectorcardiogram will help to differentiate between axis deviation due to simple rotation of the heart and axis deviation due to right or left ventricular enlargement, or between abnormally large Q deflections in Lead III due to elevation of the diaphragm and similar deflections due to infarction of the posterior wall of the heart. We hope to determine also whether it will help in the detection of minor defects in intraventricular conduction which do not increase the QRS interval beyond 0.10 second.

As a tool in research, Einthoven's method of determining the direction and magnitude of the cardiac electromotive force has been of much less value than might have been anticipated. It was employed with success by Einthoven and his associates in a study of the effect of changes in the position of the heart upon the form of the electrocardiogram. Lewis attempted to correlate the direction of rotation of the electrical axis with the order of activation of the muscle of the contralateral ventricle in bundle branch block. This study and a similar investigation in which he attempted to explain how preponderant hypertrophy of one ventricle produces characteristic changes in the form of the ventricular complex seemed for a time so well-founded as to defy criticism. Subsequent events have shown, however, that many of his conclusions cannot be accepted. It is apparent that the method is one that must be used with due regard for what it can and what it cannot be expected to accomplish. We agree with Lewis that the direction of the cardiac vector at a given instant during the QRS interval and the direction in which the excitatory process is spreading through the ventricular muscle at the same moment are very nearly if not exactly the same. When one attempts, however, to make use of this principle he is faced with a great many difficulties. One of the most serious is the lack of much more complete knowledge than we now possess regarding the spread of the excitatory process over the cardiac muscle. Another difficulty arises from the circumstance that the cardiac vector is a resultant; it is the vector sum of a great many components concerning which it gives us no information. It may well be that none of these components has the same direction as their sum, and consequently that no part of the cardiac muscle is undergoing activation in the direction which the cardiac vector defines. We are handicapped also because we are dealing solely with those components of the heart's electromotive force which lie in the plane defined by the three standard leads. In spite of these difficulties, it is possible that the vectorcardiogram may help us to learn more about

the origin of the electrocardiographic deflections and of the changes in form which they display in various types of cardiac disease. We should like to point out that it may be used in studying the relations between the QRS complex and the T deflection. It is clear that if the excitatory process were uniform in all parts of the ventricular muscle, so that the order of ventricular activation and the order of ventricular deactivation were identical, the direction of rotation of the cardiac vector during the inscription of the QRS loop and the direction of its rotation during the inscription of the T loop would necessarily be the same. When one of these loops is positive and the other negative, as in Fig. 10, it is evident that the form of T was not purely a consequence of the form of QRS, but was determined in part by local variations in the excitatory process.

SUMMARY

The cathode-ray tube affords an easy means of recording the magnitude and direction of the electromotive force produced by the heartbeat throughout the cardiac cycle. A method employed for this purpose is described. The curves obtained by this method are vector functions of the time and may be called vectorcardiograms. A number of different ways in which these curves may prove useful in teaching, in cardiac diagnosis, and in research are discussed.

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MEASUREMENT OF CIRCULATION TIMES AND THE AGENTS USED IN THEIR DETERMINATION*†

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SINCE the early work of Blumgart and his associates (1927),[1-5] increasing attention has been given to the determination of the velocity of blood flow. Fundamentally, measurement of the velocity of blood flow, or circulation time, requires the introduction of a foreign substance into the blood stream at one point and the subjective or objective perception of the time of its arrival at another part of the body. Blumgart,[6] Tarr and his associates,[7] and Fishberg[8] have reviewed in detail the steps in the development of this procedure, beginning with Harvey's description of the circulation of the blood.

In 1927 Blumgart, Yens, and Weiss[1, 2] described the use of a radium salt for measuring blood velocity. Their method was entirely too expensive and complicated for ordinary use and could not be repeated oftener than every four hours. Weiss, Robb, and Blumgart[9] attempted to measure the velocity of blood flow with histamine hydrochloride. This test, however, was accompanied at times by severe reactions and could not be used in patients with cardiac disease, in negroes, or in patients with severe anemia. Lian and Barras,[10, 11] in 1930, reported their observations with fluorescein and explained the clinical applications of the test. Kohler and other European observers began to use calcium chloride but found that leakage of this substance into the subcutaneous tissue caused sloughs. Attempts were also made to use sodium cyanide,[12] but this method, like that involving the injection of a radium salt, is objectionable because of its lack of simplicity.

A step forward was made in 1933, when Tarr, Oppenheimer, and Sager[7] improved on the method that Winternitz, Deutsch, and Bruell used in Germany. This consisted of the intravenous injection of a 20 per cent decholine sodium solution. The method was simple and merely required the measurement of the time elapsing from the beginning of the injection until the patient noticed a bitter taste. Later that year, Fishberg, Hitzig, and King[13] used soluble saccharin, the end point of this test being the appearance of a sweet taste. In 1935 Hitzig[14, 15] went even further and, with the introduction of the ether test, enabled us for the first time to measure with ease, both subjectively and objectively, the circulation time from the antecubital veins to the pulmonary capillaries.

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Goldberg,[16] in 1936, suggested calcium gluconate as a means of measuring the circulation time; with this substance the end point is a hot feeling in the back of the tongue and throat. Table I lists the different normal circulation times obtained by various observers.

TABLE I

OBSERVERS	YEAR	METHOD	DISTANCE MEASURED	RANGE (SEC.)	AVERAGE (SEC.)
Blumgart, Weiss[2]	1927	Radium C	Arm to arm	15-24	18.0
Lian, Barras[10, 11]	1930	Fluorescein	Arm to arm		30.0
Weiss, Robb, Blumgart[9]	1929	Histamine	Arm to face	13-30	23.0
Bartels, Powelson[19]	1929	Histamine	Arm to face	15-25	
Robb, Weiss[12]	1933	Sodium cyanide	Arm to carotid	9-21	15.6
Tarr, Oppenheimer, Sager[7]	1933	Decholine	Arm to tongue	10-16	13.0
Fishberg, Hitzig, King[13]	1933	Saccharin	Arm to tongue	9-16	
Lian, Facquet[17]	1936	Saccharin	Arm to tongue	8-16	
Webb, Sheinfeld, Cohn[20]	1936	Saccharin	Arm to tongue		10.7
Goldberg[16]	1936	Calcium gluconate	Arm to tongue	10-16	12.5
Spier, Wright, Saylor[21]	1936	Calcium gluconate	Arm to tongue	7-22	14.6
Baer, Slipakoff	1937	Saccharin	Arm to tongue	9-16	12.6
Baer, Slipakoff	1937	Calcium gluconate	Arm to tongue	9-16	12.7
Blumgart, Weiss[2]	1927	Radium C	Pulmonary circulation	5-17	10.8
Robb, Weiss[12]	1930	Sodium cyanide	Crude pulmonary time	7-14	10.6
Blumgart, Weiss[2]	1927	Radium C	Arm to right heart	2-14	6.7
Hitzig[14]	1935	Ether	Arm to lung	3-8	5.5
Webb, Sheinfeld, Cohn[20]	1936	Ether	Arm to lung	4-8	6.3
Lian, Facquet[17]	1936	Ether	Arm to lung	4-8	
Baer, Slipakoff	1937	Ether	Arm to lung	4-8	5.7

A review of the subject indicated that the saccharin, calcium gluconate, and ether methods should be simplest and most accurate. It was therefore decided to repeat some of the observations previously made and to compare the agents used in determining the circulation time in human beings. All of the objective methods used thus far have the distinct disadvantage of being dangerous, too complicated, or too difficult to perform at the bedside.

PROCEDURE

The experiments were performed on patients in the medical and obstetric wards, on private patients, and on patients in the cardiac, allergic, and pulmonary outpatient departments.

Each patient was made to lie in bed, and the test was not begun until the pulse and respiratory rates reached basal levels. The saccharin arm-to-tongue test was then performed, with some slight modifications of the method described by Fishberg, Hitzig, and King.[13] Rather than prepare the material anew each time a test was done, 55 gm. of powdered pure saccharin were dissolved in 50 c.c. of sterile distilled water and introduced under aseptic precautions into a rubber-stoppered sterile vial. Some of the saccharin in this solution crystallized upon cooling, but it was readily redissolved just before use by placing the vial in warm water. This preparation was stable and could be used repeatedly. After heating it to body temperature, 2.5 c.c. were drawn into a 5 c.c. syringe. With the arm at the level of the right auricle (5 cm. below the plane of the manubriosternal junction), the

solution was injected with an 18-gauge needle into the antecubital vein. The circulation rate was timed by a stop watch, from the beginning of the injection to the first moment a sensation of sweetness was noticed on the back of the tongue.

Following this, with the needle remaining in the vein, a syringe containing 5 c.c. of 20 per cent calcium gluconate was inserted into the needle. The intravenous injection of 2 to 3 c.c. of calcium gluconate causes a sudden sensation of heat in the back of the throat and tongue. The feeling of heat then spreads to the face, abdomen, perineum, and extremities. The injection is timed from the second it is begun to the instant the sensation of heat is felt in the throat. Duplicate readings were usually made with the remainder of the 5 c.c.

Finally, with the same needle *in situ*, or by another venipuncture, the ether arm-to-lung time was determined. This test was originally described by Hitzig[14] and modified slightly by Miller.[22] A mixture of 5 minims of ether and 5 minims of saline is injected intravenously; the end point is the perception of ether vapor in the upper respiratory passages. Almost invariably the patient will cough or denote by his facial expression the presence of the ether. This test is objective as well as subjective, for the observer close to the patient recognizes the odor as promptly as the patient does.

All circulation rates are recorded in seconds and are timed by stop watch from the beginning of the injection to the moment the end point is recognized.

REACTIONS

It might not be amiss to consider the question of reactions to these tests. The literature has contained references to the possibility of serious reactions accompanying the intravenous administration of calcium gluconate, but no death has been reported incidental to its use in studying the circulation time. In our series of approximately 150 injections of 2 to 5 c.c. of 20 per cent calcium gluconate, we observed but one reaction. The initial injection of calcium gluconate in a case of myocardial infarction (Case 109) was productive of severe precordial pain. In no other case was a similar occurrence noted. Saccharin is likely to cause pain in the arm when it is injected outside the vein, and a number of patients develop thrombosis of the injected vein. Leinhoff[23] reported a severe antecubital inflammatory process lasting five weeks that resulted from the perivascular infiltration of saccharin.

The injection of ether produced a creeping feeling along the course of the vein, particularly if the same vein had been used for the saccharin test. Hitzig[15] advised against introducing saccharin and ether into the same vein because of the increased number of thromboses and the greater local pain. Leinhoff[23] reported a fatality accompanying the injection of 2.5 c.c. of 10 per cent ether in saline. He doubted whether the test alone was the cause of death but felt that it was a precipitating factor.

CIRCULATION TIMES IN VARIOUS CONDITIONS

Normal Circulation Times.—In Table II are listed the circulation times of 21 patients having no known cardiac or pulmonary disease. Tests 1, 19, and 45 were performed on a patient in the maternity ward.

Greenstein and Clahr[24] and Cohen and Thomson[25] have shown that despite some minor variations the circulation time during pregnancy falls within normal limits. These determinations were therefore included among the normal times.

TABLE II

CASE	DIAGNOSIS	ETHER	SACCHARIN	CAL. GLUC.	SACCHARIN ETHER DIFFERENCE	CAL. GLUC. ETHER DIFFERENCE	ECG	COMMENTS
1	Pregnancy	5.2		14.0		8.8	Normal	Twins; dyspnea; double mitral murmur
13	Influenza	5.0	16.0	12.5	11.0	7.5		Fever, tachycardia
16	Acute pyelitis	6.0	15.0	15.0	9.0	9.0		Pyelitis
19 (1A)	Pregnancy (Post partum)	4.1					Normal	Chest clear, no dyspnea
24	Nephritis	5.0	7.5	11.0	2.5	6.0		Anasarca; no dyspnea
30	Ulcerative colitis	6.0	14.0	13.0	8.0	7.0		Diarrhea
32	Renal calculus	6.0	12.0	15.0	6.0	9.0		Urinary symptoms; obesity; dyspnea on effort
40	Ulcerative colitis	8.0	15.5	14.0	7.5	6.0		Diarrhea
45 (1B)	Pregnancy (Post partum)	5.0	12.0		7.0			No congestive signs
49	Colitis	4.7	11.0	10.0	6.3	5.3		Diarrhea
60	Nephritis	5.0	13.0	10.0 10.5	8.0	5.2		Urinary changes
61	Gastrointestinal study	5.0	13.0	12.0 14.0	8.0	8.0		Gastrointestinal symptoms
62	Acetanilid poisoning	7.0		16.0		9.0	Normal	Extreme cyanosis
83	Diabetes mellitus	5.0	8.0	8.0	3.0	3.0	Myocardial depression	Suggestion of basal râles
84	Carcinoma of stomach	5.0	14.0	15.0	9.0	10.0		No congestive signs
85	Pyonephrosis	8.0		16.0		8.0		No signs of cardiac disease
105	Polycystic kidneys	5.0		11.5 11.5		6.5		No congestive signs
121	Duodenal ulcer	6.0		12.0 12.0		6.0		
122	Buerger's disease	5.0	13.0	11.0 11.0	8.0	6.0	Normal	No cardiac signs or symptoms
131	Empyema of gall bladder	9.0		13.5 14.0		4.7	Normal	No congestive signs
134	Gastrointestinal study	6.0		15.0 15.0		9.0		No congestive signs
21 cases	Average	5.7	12.6	12.7	7.1	7.1		

The ether arm-to-lung time is an index of the functional activity of the right heart.[14, 15] In 20 of the 21 measurements the circulation time varied between 4.1 and 8 sec., with an average of 5.7 sec. In only 3 of the group did it deviate from the average by more than 1.5 sec. The end point was always sharp and in no case did we fail to get an accurate, clear-cut result.

The saccharin and calcium gluconate tests both measure the time required for the injected material to pass from the point of injection to the tongue. Since the blood velocity from the aorta to the tongue is very rapid, the difference between the ether time and arm-to-tongue time is an accurate index of the rate of flow through the left heart. This estimation of the left heart time is one of the best methods available for measuring the velocity of pulmonary blood flow.

In 30 determinations of the normal saccharin and calcium gluconate times, the range was 9.0 to 16.0 sec., as found by Fishberg, Hitzig, and King,[13] Oppenheimer and Hitzig,[26] and Goldberg.[16] The average for saccharin was 12.6 sec., for calcium gluconate, 12.7 sec. All but 3 of the determinations fell within the normal range, and repeated tests rarely varied more than 0.5 to 1.0 sec. The average left heart time was 7.1 sec., irrespective of whether saccharin or calcium gluconate was used. In Cases 24 and 83, the total circulation times were more rapid than normal. Causes of increased velocity of blood flow will be discussed later in this paper.

Circulation Time in Pulmonary Disease.—In Table III are listed determinations of circulation time in 20 patients having acute or chronic lung disease with no known cardiac complications. The circulation times were normal in all except 4 cases. One patient, a 17-year-old girl with massive recurrent empyema (Case 48), had a rapid circulation time. Hitzig[15] stated that when the circulation is obstructed in one lung, the circulation time is either rapid or in the low normal limits. Three patients (Cases 53, 54 and 99) had prolonged circulation rates. The first two had chronic tuberculosis and emphysema, and the last was a 60-year-old man who had suffered from hay fever for twenty-seven years. With these few exceptions, the left and right heart times were normal in pulmonary disease unaccompanied by cardiac changes. Oppenheimer and Hitzig[26] pointed out that uncomplicated pulmonary insufficiency is usually attended by normal circulatory measurements. They found no parallelism between the severity of clinical symptoms and the slowing of pulmonary blood flow. Even in their patients with pure right heart failure the clinical symptoms appeared out of proportion to the degree of retardation of circulation through the lungs.

Circulation Times in Cardiovascular Disease.—Table IV includes over 200 circulation times measured on 78 patients with known or suspected cardiac disease. Blumgart and Weiss[3] stated that prolongation of the circulation time almost invariably indicated the presence of congestive heart failure. Tarr, Oppenheimer, and Sager[7] found the average velocity of blood flow for patients with congestive failure to be 26 sec., which is just double the normal average.

Of the 78 patients whom we studied, 25 showed some prolongation of the ether time. In 20, or 80 per cent of these, there was definite evidence of right-sided heart failure. Of the remaining 5, one had

auricular flutter, 2 auricular fibrillation, and 2 heart block. According to Hitzig[15] and others, the ether time is normal with few exceptions, unless there is evidence of right-sided cardiac insufficiency.

In this group of 78 cardiac patients, 37, or almost 50 per cent, showed some prolongation of the left heart time, and there was no definite correlation between this prolongation and the clinical aspects of their disease. In their study of the circulatory dynamics in myocardial infarction, Fishberg, Hitzig and King[27, 28] showed that the circulation time may be normal despite the presence of extreme shock, dyspnea, and cyanosis. We have repeatedly obtained normal measurements in cases of myocardial infarction.

TABLE III

CASE	DIAGNOSIS	ETHER	SACCHARIN	CAL. GLUC.	SACCHARIN ETHER DIFFERENCE	CAL. GLUC. ETHER DIFFERENCE	ECG	COMMENTS
17	Pyopneumothorax	5.0	13.0	11.1	8.0	6.1		Unilateral functioning lung
33	Lung abscess	7.0	15.0	13.0	8.0	6.0		Cough, expectoration; hemoptysis; no râles
48	Empyema	2.5	8.0	7.5	5.5	5.0		Dyspnea; cough
53	Tuberculosis	10.0	15.0	13.5	5.0	3.5		Dyspnea; cough
54	Pulmonary tuberculosis	9.0	21.0		12.0			Dyspnea; also had emphysema
65	Acid fast contact	7.0	12.0	10.0	5.0	3.0		Cough
68	Pneumonia	6.0	14.0	9.0	8.0	3.0		Pain, cough, fever
92	Bronchial asthma	5.0		8.0 8.0		3.0		Chest clear
93	Bronchial asthma	5.0		9.0 9.0		4.0		Râles; dyspnea
94	Bronchial asthma	6.0		10.0 13.0		5.5		Râles, whines, dyspnea
95	Bronchial asthma	6.0	18.0	16.0 16.0	12.0	10.0		Normal during tests
96	Bronchial asthma, emphysema	6.0	11.0	13.0 14.0	5.0	8.5		Few râles
97	Sinusitis, asthma	6.0	15.0	11.5 13.0	9.0	6.5		Râles at bases
98	Sinusitis, asthma	5.0	15.0 16.0	13.0	10.5	8.0		Râles between attacks
99	Acute asthma	7.0	21.0	16.0 20.0	14.0	11.0		Dyspnea; hay fever, asthma
100	Bronchial asthma	5.0	12.0	9.0 9.0	7.0	4.0		Status asthmaticus
102	Bronchial asthma	5.5		11.5 13.0		6.8		Râles, wheezes
110	Lobar pneumonia	4.0	16.0	11.0 11.0	12.0	7.0		Physical signs of pneumonia
119	Bronchial asthma	5.0	9.0	9.0 9.0	4.0	4.0	Normal	Râles
120	Tracheobronchitis	5.0	11.0	11.0 12.0	6.0	6.5		Chest clear
Average		6.1	14.1	11.5	8.1	5.9		

TABLE IV

CASE	DIAGNOSIS	ETHER	SACCHARIN	CAL. GLUC.	SACCHARIN ETHER DIFFERENCE	CAL. GLUC. ETHER DIFFERENCE	ECG	COMMENTS
2	Complete heart block	18.0		55.0		37.0	Heart block; severe myocardial disease	Heart failure; extreme cyanosis
3	Cardiac failure	14.2		85.2		71.0	Myocardial failure	Anasarca; extreme dyspnea
4	Sympathicotonia	5.2	9.8	12.8	4.6	7.6	Tachycardia	Flushes; dyspnea; tachycardia; loss of weight
5	Mitral stenosis	5.4	9.8	9.8	4.4	4.4	Normal	Fatigue; dyspnea at times
6	Arteriosclerotic heart disease	12.2	23.0 22.0	32.0	10.5	19.8	Myocardial disease	Dyspnea on effort
7	Cardiac failure	19.0	26.0		7.0		Auricular fibrillation, myocardial disease	Cyanosis; dyspnea, ascites; venous stasis
8 (3A)	Cardiac failure	11.0	24.0		13.0			Obvious cardiac failure
9	Hypertension	9.2	17.3	14.3	8.1	5.1	Normal	Dyspnea on effort
10	Emphysema; heart failure	14.0	25.0	32.4	11.0	18.4	Left axis deviation	Asthmatic, musical râles
11	Neurocirculatory asthenia	5.0	11.2	9.4	6.2	4.4	Left axis deviation	Precordial pain
12	Congenital heart disease	6.0	11.0	8.5	5.0	2.5	Sinus arrhythmia	Mod. dyspnea on effort
14	Coronary artery disease	?	35.0	25.0			Myocardial disease	Hypertension; râles, precordial pain
15	Myocardial infarction	3.0	26.0 22.0		19.0		Auricular flutter	Cyanosis, tachycardia
18	Arteriosclerotic heart disease	8.0	35.0	26.0	27.0	19.0	Healed myocardial infarction	Cyanosis, dyspnea, râles
20	Severe mitral stenosis	12.0	?	?			Rheumatic disease	Dyspnea, numerous râles
21	Auricular fibrillation	15.0	26.0		11.0		Auricular fibrillation	Dyspnea; hypertension; râles, edema of feet
22	Mitral valvulitis	12.5	27.0		15.0		Auricular fibrillation	Dyspnea; cough; wheezes
23 (7A)	Cardiac failure	10.0	20.0	23.0	10.0	13.0	Auricular fibrillation	Cardiac failure less than on previous test
25	Hypertension, diabetes	5.0	15.0	12.0	10.0	7.0	Coronary sclerosis	No congestive signs
26	Hypertensive heart disease	5.0	15.0	11.0	10.0	6.0	Normal	Precordial pain; dyspnea
27	Hypertension	7.0	13.5		6.5		No evidence of myocardial disease	Palpitation
28	Mitral stenosis	10.0	26.0	21.0	16.0	11.0	Auricular fibrillation	Occasional dyspnea, no râles
31	Diabetes	7.0	30.0	26.0	23.0	19.0	Myocardial degeneration	Râles in chest; loss of appetite; abdominal pain

TABLE IV—CONT'D

CASE	DIAGNOSIS	ETHER	SACCHARIN	CAL. GLUC.	SACCHARIN ETHER DIFFERENCE	CAL. GLUC. ETHER DIFFERENCE	ECG	COMMENTS
34	Arteriosclerotic heart disease	9.0	30.0	23.0	21.0	14.0	Severe myocardial disease	No congestive signs; dyspnea on effort
35	Rheumatic endocarditis	5.0	15.0	11.0	10.0	6.0	Right axis deviation	Precordial pain
36	Coronary artery disease	7.0		14.0		7.0	Myocardial degeneration	No congestive signs
37	Aortic and mitral stenosis	8.0		14.0		6.0	Left axis deviation	Marked kyphoscoliotic chest deformity
38	Coronary occlusion	5.0	28.0	28.0	23.0	23.0	Myocardial infarction	Dyspnea, râles, cyanosis
39	Myocarditis	7.0	40.0		33.0		Heart block; severe myocardial disease	Orthopnea, râles, pleural effusion
42	Hyperthyroidism	10.0	26.0	18.0 20.0	16.0	9.0	Auricular fibrillation	Râles at bases
43	Rheumatic endocarditis	5.5	14.5	13.5	9.0	8.0	Normal	No congestive signs
44	Rheumatic endocarditis	11.5	18.5	19.0	7.0	7.5	Suggestive of rheumatic endocarditis	Dyspnea; no decompensation
46	Arteriosclerotic heart disease	6.0	35.0	26.0	29.0	20.0	Normal	Dyspnea; palpitation; edema
47	Arteriosclerotic heart disease	9.0	17.0	14.0	8.0	5.0	Left axis deviation	Dyspnea, precordial pain
50	Coronary disease	6.0	23.0	15.5	17.0	9.5	Severe myocardial disease	Precordial pain; palpitation; dyspnea
52	Auricular fibrillation	8.0		20.0		12.0	Extrasystoles	Dyspnea; palpitation
55	Thyrotoxicosis	6.0	13.0	21.0	7.0	15.0	Normal	Palpitation
56	Arteriosclerosis	5.5	16.0	12.0	10.5	6.5	Myocardial disease	Dyspnea; precordial pain
57	Rheumatic fever	5.2		10.0		4.8	Tachycardia	No congestive signs
58 (52 A)	Auricular fibrillation	6.6	22.0		16.4		No myocardial disease	Anemia; dyspnea on effort
59	Hypertension	5.0	12.0	11.0	7.0	6.0	Coronary sclerosis	No congestive signs
63	Rheumatic carditis	7.0		23.0	16.0		Auricular fibrillation	Cardiac failure
66	Hypertension	8.0	18.0	21.0	10.0	13.0	Myocardial disease	Dyspnea on effort
67	Coronary sclerosis	8.0		13.0		5.0	Myocardial disease	Precordial pain only
69 (15 A)	Coronary occlusion	7.0	21.0	13.5	14.0	6.5	Acute infarction	No evidence of failure
70	Coronary occlusion	4.0	20.0	17.0	16.0	13.0	Myocardial infarction	No evidence of failure
72	Coronary disease	9.0	30.0	20.5	21.0	11.5	Coronary sclerosis	Bradycardia
73	Rheumatic endocarditis	6.0	10.0	11.0	4.0	5.0	Normal	Normal
74	Mitral stenosis	8.0	54.0	45.0 43.0	46.0	36.0	Auricular fibrillation; intraventricular conduction defect	Dyspnea on minor effort

TABLE IV—CONT'D

CASE	DIAGNOSIS	ETHER	SACCHARIN	CAL. GLUC.	SACCHARIN ETHER DIFFERENCE	CAL. GLUC. ETHER DIFFERENCE	ECG	COMMENTS
75	Angina pectoris	4.0	12.0	10.0	8.0	6.0	Coronary sclerosis	No congestive signs
76	Tachycardia	15.0	34.0	25.0	19.0	10.0		Dyspnea; râles in chest
77	Myocarditis	5.0	13.0	15.0	8.0	10.0	Normal	No congestive signs
82	Cardiac disease	14.0	38.0	28.0 22.0	24.0	12.0	Myocardial disease	Dyspnea; râles; old coronary occlusions
86	Hypertension	4.0	10.0 10.0	10.0	6.0	6.0	Myocardial disease	Precordial pain
87	Arteriosclerotic heart disease	4.0	18.0	14.0 16.0	14.0	11.0	Myocardial disease	No signs of decompensation
88	Mitral regurgitation	6.0		16.0 16.0		10.0	Normal	No congestive signs
89	Coronary occlusion	8.0	20.0	16.0 24.0 ?	12.0	12.0	Coronary occlusion	Dyspnea; cyanosis
90	Possible coronary occlusion	7.0	15.0	15.0 13.0	8.0	7.0	Normal	Few râles on admission
101	Healed coronary occlusion	8.0		25.0 26.0		17.5	Myocardial disease	Dyspnea on moderate effort
107	Rheumatic endocarditis	7.0		15.0 18.0		9.5	Myocardial disease	No congestive signs
109	Coronary occlusion						Acute occlusion	Severe pain on injection of calcium
111	Hypertension	8.5		12.0 14.0		4.5	Negative	Precordial pain
112	Myocarditis	7.0		14.0 14.0		7.0	Myocardial disease	No congestive signs
114	Hypertension	6.0		10.0		4.0	Myocardial disease	No congestive signs
115	Coronary occlusion	7.5	18.0 ?	15.5 16.5	10.5	8.5	Acute infarction	Precordial pain
116	Coronary occlusion	14.0	36.0	22.0 26.0	22.0	10.0	Acute infarction	No congestive signs
117	Sciatica	11.0	27.0	20.0	16.0	9.0	Myocardial disease	Râles at bases
123 (16 A)	Coronary occlusion	14.5	18.5	18.0 18.0	4.0	3.5	Coronary occlusion	Precordial pain
124	Arteriosclerotic heart disease	8.0	16.0	15.0	8.0	7.0	Myocardial disease	Râles at bases
125	Arteriosclerosis	8.5	16.0	15.0 18.0	7.5	8.5	Myocardial disease	No signs of decompensation
127	Coronary occlusion	6.0		14.0 14.0		8.0	Coronary occlusion	Pain
128	Cardiac failure	10.0	45.0	32.0 34.0	35.0	23.0	Severe myocardial disease	Râles in chest
130	Coronary occlusion	7.5		20.0 22.0		13.5	Severe myocardial disease	Râles; ascites
132 (128 A)	Cardiac failure	10.0		31.0		21.0	Severe myocardial disease	Râles; dyspnea
136	Healed coronary occlusion	7.0		14.0 14.0		7.0	Healed occlusion	Pain in chest
137	Hypertension	8.0		16.0 16.0		8.0	Slight myocardial disease	Dyspnea; no râles

Table V presents further interesting data. Among 46 patients having prolonged circulation times, 33, or more than 70 per cent, showed some evidence of circulatory insufficiency, but only one, or 3 per cent, of 32 patients with normal circulation times had evidence of pulmonary congestion. When circulation times and electrocardiograms were compared, it was found that more than 80 per cent of cardiac patients

TABLE V

	NUMBER	OBVIOUS FAILURE		PULMONARY CONGESTION		DYSPNEA ONLY		ABNORMAL ECG.	
Prolonged left and right heart times	23	15	65%	1	4.3%	7	30.7%	19	82.0%
Prolonged left heart time only	22	12	54%	4	18.0%	6	28.0%	19	85.0%
Prolonged right heart time only	1	1	100%					1	100%
Normal circulation times	32	0		1	3.1%	20	60.2%	15	45.5%

TABLE VI

CASE	DIAGNOSIS	ETHER	SACCHARIN	CAL. GLUC.	SACC. ETHER DIFFER.	CAL. GLUC. ETHER DIFFERENCE	ECG	COMMENTS
41	Hemiplegia, polycythemia	6.0	20.0	18.0	14.0	12.0		Hemiplegia; no congestive signs
71 (41A)	Hemiplegia, polycythemia	13.0	27.0	20.0	14.0	7.0		Hemiplegia; cyanosis
80	Toxic goiter	5.0	10.0	9.9 9.0	5.0	4.0		No congestive signs
81	Gastric ulcer	6.0	25.0?	18.0 25.0	19.5	15.5		Poor myocardial tone; dehydration
91 (81A)	Gastric ulcer	6.0	25.0?	13.0 20.0	19.0	10.5	Suggestion of myocardial disease	No congestive phenomena
106 (41B)	Polycythemia	7.0		18.0 16.0		10.5		Markedly cyanotic
129	Hyperthyroidism	5.5	9.0	8.0 9.0	4.5	4.0	Tachycardia	No congestive signs
135	Hyperthyroidism			8.0 9.0				Nervousness; tremors

with prolonged circulation times showed electrocardiographic changes indicative of myocardial disease. Of the patients with normal circulation times only 45.5 per cent showed similar changes.

Other Causes for Abnormal Circulation Times.—A few patients with abnormal circulation times had no obvious heart disease (Table VI). Tests 41, 71, and 106 were performed at various times on a patient with polycythemia and hemiplegia. The prolongation of the circulation time was undoubtedly due to the polycythemia, for similar observations have

been made by Blumgart, Cowgill and Gilligan,[29] Tarr and his co-workers,[7] Webb and his co-workers,[20] and Hitzig.[15]

The circulation time also parallels the basal metabolic rates. Blumgart[6] showed that the velocity of blood flow was strikingly increased in thyrotoxicosis and slowed in myxedema, and others[7, 20, 30, 31] have reported similar observations. Goldberg[16] used the calcium gluconate time as a test for hyperthyroidism. In three cases of hyperthyroidism (Cases 80, 129, and 135), we found the arm-to-tongue times rapid or in the low normal range. It has been suggested[7] that a normal circulation time in the presence of undoubted clinical signs of heart failure should make one search for factors tending to increase the velocity of blood flow. Tarr, Oppenheimer and Sager[7] found that the average decholine time in cases of hyperthyroidism with failure was 13 sec.

Other causes for an increase in the velocity of blood flow have been reported. A rapid ventricular rate may at times be associated with a definite increase in the velocity of pulmonary blood flow.[6] Kopp[32] found that the induction of therapeutic fever caused an increased circulation time. Averbuck and Friedman[33] reported that the saccharin arm-to-tongue time was somewhat more rapid in children than in adults. Ellis[34] found that exercise increased the velocity of blood flow, and others[16, 7, 29] have reported a rapid circulation time in patients with anemia.

Tests 81 and 91 remain for consideration. They were performed at different times on a 43-year-old man who was supposed to have a peptic ulcer. Though no definite myocardial insufficiency could be found, the arm-to-tongue times were prolonged. Operation and incomplete postmortem study later revealed linitis plastica and very severe atheromatous changes in the aorta.

DISCUSSION

Apparently the most satisfactory method of measuring the velocity of blood flow is by the ether and calcium gluconate methods.

In the studies on normal patients and those presenting uncomplicated pulmonary disease (Tables II and III), there is a satisfactory correlation between the arm-to-tongue times as obtained by the calcium gluconate and saccharin methods, but this is not the case in those with cardiac disease (Table IV). The saccharin time in this later group was frequently from 3 to 10 sec. longer than the calcium gluconate time. The discrepancy was most marked in those cases showing prolonged circulation rates, perhaps due to the sharper end point obtained with calcium gluconate.

There remain for our consideration some of the clinical applications of those procedures. Table V shows that approximately 30 per cent of cardiac patients with prolonged circulation times did not have obvious heart failure. Some were not examined in detail because of our

unwillingness to disturb patients with acute myocardial infarction. Perhaps more careful study would have revealed the presence of some degree of circulatory embarrassment. But it is precisely in this group that measurement of the circulation time is most instructive. Blumgart and Weiss[4, 35, 36, 37] pointed out that retardation in the velocity of blood flow may precede clinical evidence of heart failure. Hitzig[15] showed that the ether time may be prolonged in certain cases of left heart failure with incipient right heart failure. A number of cases can be cited from our records in which prolongation of the circulation time predicted the onset of cardiac failure. For example, a patient (Case 15) had acute myocardial infarction. A circulation test which was performed while he had auricular flutter but seemed perfectly compensated revealed a definite prolongation of the left heart time. The following day he developed obvious signs of extreme circulatory embarrassment (cyanosis, edema, orthopnea, and bilateral pleural effusion).

These tests can be used to detect not only the onset, but also the type, of circulatory failure. This is of considerable practical value, for, as Fishberg, Hitzig and King[28] have pointed out, the ability to differentiate between right and left heart failure is necessary if patients suffering from myocardial infarction are to be treated rationally.

Webb, Sheinfeld, and Cohn[20] have measured the circulation rates in a large number of surgical cases and found that those patients with prolonged circulation times were poor operative risks and had a high operative mortality rate. They used the test also in differential diagnosis of cardiac, pulmonary and intraabdominal disturbances, but these results must be interpreted with caution, for in many cases of myocardial infarction and severe myocardial disease the circulation times are normal while the patient remains in bed. It must be remembered that the circulation time test is only a measure of the velocity of blood flow; obviously, it cannot tell us how much work the heart can do.

All in all, we believe that the measurement of arm-to-lung and arm-to-tongue times leads to more accurate diagnosis, particularly of cardiac and pulmonary disease, as Oppenheimer and Hitzig[26] and Weiss and Kleinbart[38] have shown. The value of the procedure in studying anemia and disturbances of metabolism has already been mentioned.

SUMMARY AND CONCLUSIONS

The ether arm-to-lung time of 21 patients with no evidence of cardiovascular disease ranged from 4 to 8 sec., with an average of 5.7 sec. Normal saccharin and calcium gluconate arm-to-tongue times varied from 9 to 16 sec., with an average of 12.6 and 12.7 sec., respectively. The normal left heart time averaged 7.1 sec.

Circulation times in 20 patients suffering from uncomplicated bronchial or pulmonary disease fell within normal limits.

The presence of a normal circulation time almost invariably precluded the existence of congestive heart failure.

More than 70 per cent of 46 cardiac patients with prolonged circulation times showed evidence of circulatory insufficiency. Only 1, or 3 per cent, of cardiac patients with normal circulation times had pulmonary congestion.

Polycythemia vera caused a retardation and hyperthyroidism an increase in the velocity of blood flow.

The measurement of the circulation time is an effective aid in the early diagnosis of heart failure and in the differentiation of cardiac from pulmonary and other diseases.

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CALCAREOUS AORTIC VALVE STENOSIS

With Particular Reference to Its Etiology*

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NO AGREEMENT has been reached as to the etiology of that pathologically characteristic lesion, calcareous aortic valve stenosis. The possible causes which have been suggested are (1) rheumatic fever, (2) arteriosclerosis, (3) healed subacute bacterial endocarditis, and (4) inflammatory or degenerative endarteritis of the vessels of the aortic valve ring.

We have encountered thirty-nine hearts with this lesion in a series of nine hundred consecutive autopsies. Seventeen of these hearts showed uncomplicated nodular calcification of the aortic valve leaflets; this series is designated below as series U. In twenty-two of these hearts there were varying degrees of pathologic involvement of the other valves (designated below as Series C). Sufficient consistent pathologic and clinical differences were found between these two small series to indicate a different pathogenesis for each.

PATHOLOGIC DATA

The presence of some degree of stenosis, with calcification, of the aortic valve was the original, sole criterion for selecting the hearts. In twelve of the seventeen uncomplicated cases comprising Series U the lesion was fully developed, with nodular masses of calcium markedly deforming the aortic valve and protruding into the sinuses of Valsalva. Less complete, less advanced lesions were found in the aortic valves of the other five hearts of Series U. In two of these valves two of the three leaflets were calcified and fused. In another valve the anterior cusp stood out as a single, calcified plaque, and the other two leaflets merely had a few small nodules at their bases. In two hearts the calcium deposits were confined entirely to the base of the aortic valve leaflets; the edges of the leaflets were thin.

In eleven (50 per cent) of the hearts in series "C" the marked calcification and stenosis of the aortic valve were indistinguishable from the twelve uncomplicated, fully developed lesions in Series U. The valves of the three additional hearts, all from patients over 70 years of age, resembled the five incompletely calcified valves found in Series U, i.e., the calcification was located primarily at the base of the valve leaflets.

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However, in the remaining eight hearts of Series C, in which there was incomplete calcareous aortic valve stenosis with mitral valve lesions, the character of the aortic valve lesions was significantly different. In four the calcification was confined either solely or predominantly to the free edge of the leaflets; in three it was diffusely and irregularly scattered throughout the leaflets; and in one it was in superimposed vegetations on the valve leaflets.

The complicating mitral valve lesion in Series C consisted in four instances of slight thickening of the free edge of the leaflets; nine hearts showed grossly thickened leaflets without significant stenosis; and nine showed definite mitral valve stenosis. In eleven instances there was calcification in the deformed mitral valve leaflets. Three hearts of Series C also showed some deformity of the tricuspid valve.

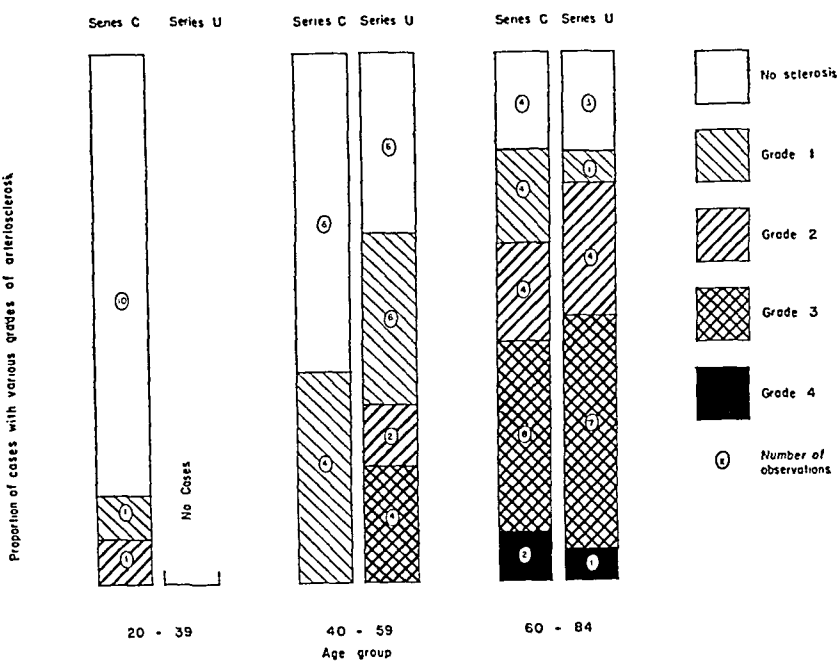

Fig. 1.—Showing the various grades of generalized arteriosclerosis in different age groups in patients with calcareous aortic valve stenosis. Series U, uncomplicated. Series C, complicated by lesions in other valves.

Pericardial adhesions were present in only two cases in Series U and in eight in Series C. In the latter series the pericardial sac was completely obliterated in two; in four the adhesions were very numerous; and in two there was but a single adhesion band.

Splenic infarcts, old or recent, were found in only four cases, all of which were in Series C.

To evaluate the amount of *generalized arteriosclerosis* present, the observations on the degree of arteriosclerosis of the coronary arteries and aorta were graded on an arbitrary scale of zero to four. Each observation was given equal weight in order to limit the number of categories into which a comparatively small number of observations (78) would be divided. Fig. 1 shows the proportion of the various

grades of arteriosclerosis in each age group of the two series. The usual increase in the amount of arteriosclerosis with age is shown in both series. Within each separate age group, however, there was more arteriosclerosis in the individuals with calcareous aortic valve changes unaccompanied by mitral valve changes (Series U) than in the corresponding individuals in Series C.

CLINICAL DATA

The *sex* and *age* distribution of these patients is shown in Table I. Among the seventeen patients in Series U there were only two women; in Series C there were eleven men and eleven women. In Series U no patients were under 40 years of age at death, and only three (18 per cent) were under 50, but in Series C eleven patients (50 per cent) were under 50 years of age.

A typical history of rheumatic fever was elicited from fourteen of the thirty-nine patients. Of the group of twenty-two patients with mitral valve involvement (Series C), thirteen gave such a history. The rheumatic fever history in the patient without mitral valve disease was not characteristic.

TABLE I

DISTRIBUTION BY AGE AND SEX

YEARS	SERIES U UNCOMPLICATED			SERIES C COMPLICATED		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
20-29	0	0	0	3	1	4
30-39	0	0	0	1	1	2
40-49	2	1	3	2	3	5
50-59	6	0	6	0	0	0
60-69	3	0	3	3	0	3
70-79	3	1	4	2	5	7
80-89	1	0	1	0	1	1
Total	15	2	17	11	11	22

DISCUSSION

The single complication of changes in the margins of the mitral valve leaflets divided our originally selected series of hearts showing calcareous aortic valve stenosis into two groups; in one the valve deformity was probably of rheumatic origin, but in the other there was no definite evidence that the etiology was rheumatic. The many differences between the two series were striking enough to suggest that we were dealing with two essentially different pathologic entities. Fig. 2 summarizes graphically the major differences between these two groups. In neither group was there any clinical or pathologic evidence of previous bacterial endocarditis, or of underlying endarteritis of the aortic ring arterioles, both of which have been suggested as possible etiologic factors (Cabot,[1] and Margolis and co-workers[2]).

Table II includes our cases, together with almost four hundred other previously reported cases of aortic valve stenosis. Definite aortic valve stenosis was present in all the cases, and, in at least some of the hearts, the valves were calcified. The reported series fell into four groups. The first group, corresponding to our Series U, includes those hearts in which there was absolutely no evidence of endocarditis of the mitral valve leaflets. In the second group some hearts might have shown slight thickening of the mitral valve leaflets. The third group is an obviously mixed group. In all of the cases of the fourth group, corresponding to our Series C, there was definite thickening of the mitral valve leaflets. In this entire collection the incidence in women and of a history of rheumatic fever increases, and the percentage of patients over fifty years of age decreases, as one proceeds from Group I to Group IV.

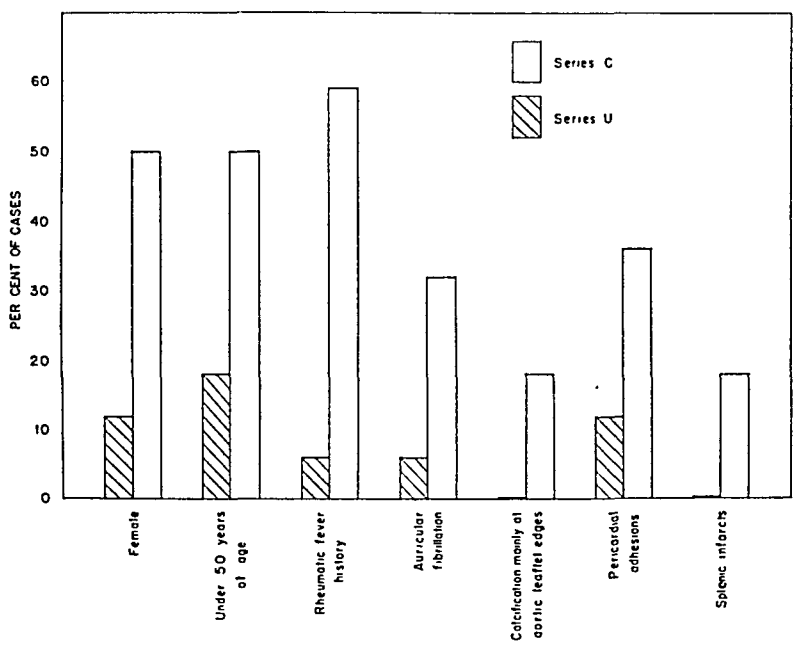

Fig. 2.—The major differences between the cases of uncomplicated calcareous aortic valve stenosis (Series U) and those of calcareous aortic valve stenosis complicated by changes in the mitral valve (Series C).

In view of the ready division of our own series into two groups with and without evidence of a rheumatic process, it was considered desirable to review the literature for evidence which might indicate that calcareous aortic valve stenosis is always due to rheumatic fever. There was a definite history of rheumatic fever in eleven (50 per cent) of Christian's twenty-two patients,[3] but he also states that "in none were the tricuspid, mitral, or plumonic valves structurally abnormal *except for occasional thickening of the leaflets.*" In Clawson's series,[4] "rheumatism, as indicated by a positive history or by evidence of a previous pericarditis or by both, was present in 49 per cent of the 160 cases of the noncalcified group (of aortic stenosis), and in 40 per cent of the 93 cases of the calcified nodular valve deformity." He also adds that 38

TABLE II

REPORTED CASES OF CALCAREOUS AORTIC STENOSIS CLASSIFIED ACCORDING TO AGE, SEX, AND HISTORY OF RHEUMATIC FEVER

	TOTAL CASES IN SERIES	FEMALES		OVER 50		HISTORY OF RHEUMATIC FEVER		CRITERIA			AUTHOR
		NO.	%	NO.	%	NO.	%	AORTIC CALCIFICATION	NON-STENOTIC MITRAL LESION	MITRAL STENOSIS	
Group I	12	1	8	10	83	0	0	P*	A	A	Gibbs[10]
No cases in which there was thickening of mitral leaflet edges	15	1	5	12	80	2	13	P	A	A	Clawson[5]
	17	2	12	14	82	1	6	P	A	A	Series U
Group II	42	8	19	35	83	3	7	P	I	A	Margolis[2]
Possibly mixed series	45	19	20	34	76	8	18	P	I	A	McGinn[6]
	59			36	61			P	I	A	Clawson[4]
	21	6	29	13	62	11	52	P	M	A	Christian[3]
	28	3	9	15	54	14	50	P	M	A	Cabot[1]
Group III	35	7	20	16	46	9	26	M	A	A	McGinn[6]
Probably mixed series	86	17	20	52	60	32	37	P	M	M	McGinn[6]
	93			49	53	46	49	P	M	M	Clawson[4]
Group IV	15	8	52	3	20	9	60	M	P	M	Gibbs[10]
All cases in which there was thickening of mitral leaflet edges	22	11	50	11	50	13	59	P	P	M	Series C
	34			13	38			P	P	M	Clawson[4]
	50	21	42	11	22	37	74	M	P	P	McGinn[6]
	40	13	33	14	35			M	P	P	Cabot[1]

*P, present in all cases; A, absent in all cases; M, mixed, present in some cases; and I, indeterminate, data insufficient.

patients (41 per cent) in the calcified nodular group had, in addition, acute or healed lesions of the mitral valve. In his previously reported series of fifteen cases (Clawson, Bell, and Hartzell[5]) in which there was an old, calcified, nodular deformity of the aortic valve, and, presumably, no abnormality of the edges of the other valves, there were only two patients with pericardial adhesions and two with histories of rheumatic fever.

Margolis and co-workers[2] elicited a history of "rheumatism" from but three of forty-two patients selected "on the basis of the existence, pathologically, of calcareous infiltration of the leaflets of the aortic valve in the absence of *significant degrees* of involvement of other valves." McGinn and White[6] reported that a history of rheumatism was obtained in 18 per cent of forty-five patients with aortic valve stenosis without mitral valve stenosis. Hearts with nonstenotic mitral valve lesions are not mentioned as being excluded. However, a history of rheumatic fever was obtained in 74 per cent of fifty cases of aortic valve stenosis, both calcified and noncalcified, in which definite stenosis of the mitral valve was also present.

The data in other series are not in such form as to permit division into these two groups. In our series of thirty-nine patients, thirteen (33 per cent) had a definite history of rheumatic fever, and nine additional patients (23 per cent) had mitral valve lesions which might well have been of rheumatic origin. All our patients with histories of rheumatic fever also had mitral valve changes.

In a review of 411 cases in which death was caused by rheumatic heart disease, Davis[7] found 198 hearts in which both the aortic and mitral valves were deformed, and only eighteen instances of pure aortic valve deformity. Thus, in but 8 per cent of a large number of hearts in which the aortic valves were deformed by rheumatic fever was the lesion confined to that valve. On the other hand, in Clawson's series[4] of 93 hearts with calcareous aortic stenosis, 55 (59 per cent) presumably showed no mitral valve deformity. Also, in our series of 39 hearts, 17 (44 per cent) were without rheumatic mitral valve involvement. This high incidence of pure aortic valve lesions in hearts with calcareous aortic valve stenosis suggests that rheumatic fever cannot be the sole etiologic agent.

The high incidence of pericardial adhesions in patients with calcified aortic stenosis is repeatedly offered as additional evidence that the aortic valve lesion is of rheumatic origin. In our series, however, pericardial adhesions were common only in the cases in which there was accompanying mitral valve disease.

The location of the calcification in the aortic valve cusps has been used both to support and discredit rheumatic fever as the etiologic agent. In some instances the calcium is located principally at the free edge of the leaflet, and in advanced lesions the entire cusp is calcified. This is said

to be consistent with changes subsequent to rheumatic fever. Mönckeberg,[8] and Margolis and his associates[2] emphasize the fact that in hearts without mitral valve lesions the early calcification is at the base of the aortic valve leaflets. In those of our cases in which there were rheumatic mitral valve deformities, incomplete aortic valve calcification always involved only the free edges of the leaflets, but in those in which there was no mitral valve lesion, the incomplete aortic valve calcification invariably extended from the base of the leaflets. Thus another difference is established between the two groups.

Some workers[9, 8, 10] regard arteriosclerosis as the most likely cause of calcified aortic valve stenosis. Others[3, 4] maintain that such patients have less general arteriosclerosis of the aorta and coronary arteries than other individuals of the same age. Because of the vagaries in the distribution of arteriosclerosis, such an objection does not seem valid. Gibbs[10] found a high incidence of arteriosclerosis of the aorta and renal arteries in his series. In our series the amount of generalized arteriosclerosis was roughly proportional to age. In general, more arteriosclerosis was found in the "uncomplicated" group than in the group in which there were associated mitral valve lesions, but this is very slight evidence that arteriosclerosis was the etiologic factor in the uncomplicated cases, and can be accepted only because all other possible causes were apparently excluded.

According to differences in the age and sex distribution, in the incidence of a history of rheumatic fever, of pericardial adhesions, of splenic infarcts, and of generalized arteriosclerosis, and from the location of the calcification in the earlier, incomplete lesions, cases of calcareous aortic valve stenosis can be divided into two groups: in one the lesion is rheumatic in origin and there is an accompanying deformity of the mitral valve, and in the other the lesion is uncomplicated and probably of arteriosclerotic origin.

SUMMARY

Seventeen cases of calcareous aortic valve stenosis without mitral valve deformity are compared with twenty-two cases of calcareous aortic valve stenosis in which there was an associated lesion of the mitral valve of rheumatic origin. Patients under fifty years of age, women, histories of rheumatic fever, and instances of pericarditis were scarce in the former group and numerous in the latter.

In the cases of pure aortic valve stenosis the calcification in the valves was most pronounced at the base of the cusps, whereas in some cases in the other group it was more marked at the free edges of the cusps.

A slightly higher incidence of arteriosclerosis of the aorta and coronary arteries was found in the cases of uncomplicated aortic valve disease.

Calcareous aortic valve stenosis is not always rheumatic in origin. In some cases the etiology of the lesion is probably of the nature of an arteriosclerotic degeneration.

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THE LAG-SCREEN BELT ELECTROCARDIOGRAM*

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THE need of instant and continuous viewing of electrocardiograms has always been apparent. We have designed and shall describe a simple and effective device which, when attached to the electrocardiograph, permits such continuous observation. This apparatus is portable, compact, durable, simple, adaptable to all electrocardiographs, and permits simultaneous photographic recording.

The apparatus has a moving, flexible, endless belt coated with material which phosphoresces when exposed to the light beam of the electrocardiograph. The to-and-fro motion of the beam at the viewing aperture is thus given a second dimension, and the familiar graphic form appears exactly as on bromide paper. When the viewing aperture is kept dark, the degree of phosphorescence on the moving translucent screen is sufficient to define exactly the wave form, and, inasmuch as the image is retained from 8 to 30 seconds, one may view strips from 6 to 20 inches in length, which is ample for comparisons of rhythm and wave form. A given point on the screen loses its phosphorescence before it passes again over the viewing aperture.

The major difficulties in developing the lag-screen belt were (1) to find the most suitable phosphorescent material and the means of applying it to the surface of a flexible belt; (2) to provide light of sufficient intensity to ensure good contrast; and (3) to preserve the conventional optical system and camera, so that the electrocardiogram might be viewed and photographed at the same time.

Our early experiences taught us that there was a wide discrepancy in the phosphorescent properties of minerals obtained from various sources.[1, 2] Experiments with light of different wave lengths led us to the conclusion that the materials we used phosphoresce most actively with wave lengths between 3,000 and 6,000 angstroms, which covers the visible spectrum and a portion of the ultraviolet. The problem was simplified when it was found that ultraviolet light and a special quartz lens system were not necessary. From the long list of phosphorescent materials available we selected phosphorescent zinc sulfide crystals containing the impurities which are not only essential to the physical property of phosphorescence but also determine the color of the glow.[3] The yellowish green and the yellow gave the best contrast. The material used must be selected as an individual lot; it may be obtained of

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scientific supply houses.* The crystals apparently retain their property of phosphorescence without demonstrable loss for months. It seems that the deterioration is much less than that of material subjected to the cathode ray.

We used 35 mm. motion-picture film for narrow belts and ordinary photographic film for wider ones, joining the ends together with Duco cement. We found that the best method of applying the mineral to the belt was to spray it on the softened, moist, gelatinous surface of the cleared film. The crystalline material adheres firmly on drying without loss of phosphorescent property and gives the optical effect of a beaded motion-picture screen. The coating may be made as thick as desired by painting the sprayed surface with a suspension of crystals in warm, clear gelatin. Further experiments proved that the lag, or persistence time of the image, depended on three factors: The character of the material;[4] the thickness of the coating; and the amount of energy conveyed to it by the light beam. The range of the last two factors is limited. Increasing the thickness of the belt lessens its transparency and therefore hinders the passage of the activating light beam. Thicker belts lose flexibility and are apt to flake. There is also diffusion of light in the thicker belts so that increasing the intensity of the light is not a solution of the problem of securing better definition. Practically, there is a limit to the amount of light that can be reflected from the small galvanometer mirror. An increase in the area of the galvanometer mirror is not desirable, as it introduces distortion by lowering the frequency response of the galvanometer.

We have used automobile line focus light bulbs, motion-picture projector lamps, and the 85-watt, high intensity mercury-vapor lamp of the General Electric and Westinghouse Companies, with practically the same results. The mercury-vapor lamp has the advantages of extremely high intensity in the region of the shorter wave lengths of the visible spectrum and a low heat-light ratio, but it is much larger than the others, and requires a special alternating current transformer. Despite these disadvantages we have used it when long operation was required. This high intensity mercury-vapor lamp peaks at 3,650 angstroms, which permits the use of the standard optical glass lens system. A concentrating and reflecting lens of a high order of efficiency is essential, and there is little space for mounting such a lens in electrocardiographs of the General Electric type. First-surfaced reflectors are not essential, but they will increase contrast and permit the use of smaller, internally mounted, direct current lamps.

To permit simultaneous photographic recording at selected intervals during prolonged viewing with the lag-screen we have used a special light source with an angle of incidence and reflection which is different from that of the regular electrocardiographic optical system, but this

*Pfaltz and Bauer, Empire State Building, New York City, N. Y.

does not impair the efficiency of either system; it is only a matter of changing to a one-light, split-beam arrangement. The use of the extra light permits photographic registration of a white beam and time lines, while on the lag-screen one sees a glowing line on a dark background.

Fig. 1 illustrates the method of building a lag-screen belt in a model "B" General Electric electrocardiograph; the construction of the case of this instrument lends itself ideally to this purpose. The belt emerges from the interior of the case at the viewing aperture in the right front portion, and passes along the black enameled surface to go over driving

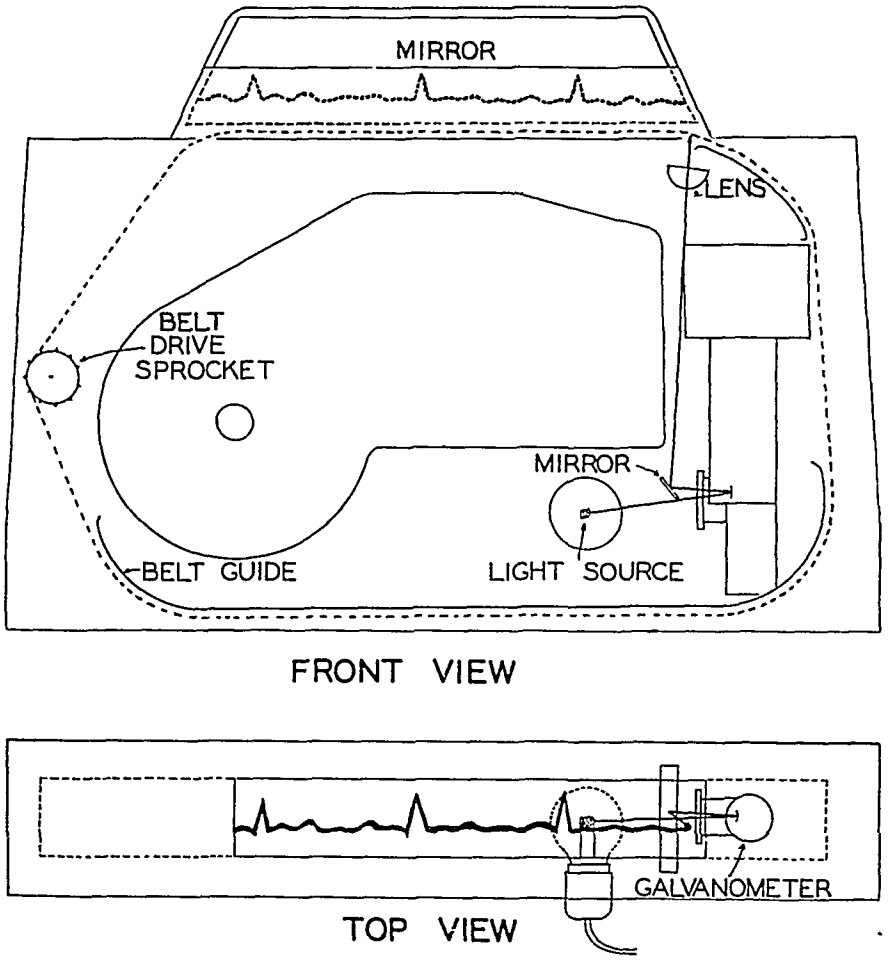

Fig. 1.—Diagram of the lag-screen belt installed in a portable electrocardiograph. The endless belt is shown passing through the viewing aperture over the surface of the top of the machine, where it is viewed in the mirror, thence over drive sprockets and guides. The viewing mirror is mounted in a light-trap. The top view shows the mirror system used for external light mounting.

wheels around the camera and the galvanometer. When so fitted, the belt is driven by the gears of the electrocardiograph motor, which is controlled as usual by the camera lever on the control board. The film drum within the camera is fitted with a drive which is engaged when a photographic tracing is desired.

The construction of a separate lag-screen viewing box necessitates passing the belt over rollers driven continuously by a synchronous motor.

A separate light source and a galvanometer actuated from the amplifier output, wired in parallel with the galvanometer of the electrocardiograph, are used. This separate unit is adaptable to machines now in use and simplifies simultaneous photography, for the camera motor may be started at any time during the viewing; the greater width of the lag-screen belt facilitates visualization in the classroom or operating room. For the larger system the most intense light source and the largest possible galvanometer mirror surface are used.

The cathode-ray lag-screen has been adapted to electrocardiography by Dr. Frank N. Wilson at the University of Michigan, and in the later commercial Dumont and Hindle instruments, but the large cathode-ray tubes which are required and the necessity of incorporating a slow-sweep beam and an automatic base line changer which interrupts the waves make the instrument difficult to transport, complicated, and expensive. Contrariwise, the lag-screen belt attachment enables one to view longer strips without changing the control or galvanometer system, is inexpensive, and does not affect portability. When a light-trap carrying a mirror ,(Fig. 1) is placed above the belt the image is upright and extraneous light is excluded.

SUMMARY AND CONCLUSIONS

The inexpensive lag-screen belt attachment which we have described makes it possible to view the electrocardiogram while it is being recorded. Immediate visualization is useful in emergencies and in teaching, saves time and expense, especially when it is desirable to make observations over long periods (e.g., during surgical or obstetrical procedures), enables the clinician to follow and record rapid changes in the mechanism of the heart beat, facilitates differentiation of the various arrhythmias, and helps to estimate the effects of drugs. The lag-screen method is analogous to fluoroscopy; fine details, such as notching of the P-waves and minor changes in the form of the QRS complex, may be missed, but these disadvantages are more than offset by the fact that it gives us a great deal of valuable information quickly.

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OBSERVATIONS ON PASSIVE VASCULAR EXERCISE AND OTHER FORMS OF TREATMENT OF PERIPHERAL VASCULAR DISEASE*

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MANY forms of therapy have been devised for peripheral vascular disease,[1, 2, 3] especially for that which leads to occlusion of arteries. The development of apparatus for passive vascular exercise by Herrmann and Reid,[4] and Landis and Gibbon,[5] was hailed with considerable enthusiasm. Those who originated the method were optimistic about the results which they obtained from this form of treatment. Other observers, notably Wilson and Roome[6] and Allen and Brown,[7] have not been encouraged by their results. As with many kinds of therapy which exert a considerable psychic effect on the patient, the latter observers believed that direct benefit from the apparatus must be cautiously evaluated. Our observations, which were begun shortly after the introduction of passive vascular exercise therapy, were also discouraging, as will be pointed out later. Another difficulty in judging the efficacy of this form of therapy is that it has, in many instances, been combined with other measures which might influence the therapeutic result. The symptoms of peripheral vascular disease are frequently so urgent and troublesome that rigid adherence to any plan of controlled observation becomes almost impossible. Because of this difficulty, and the great confusion that now exists with respect to the treatment of peripheral vascular disease, experiments were devised with the hope that some light might be thrown on the methods of re-establishing the circulation in diseased and normal legs under different conditions.

EXPERIMENTS BY PERFUSION OF EXTREMITIES

Experimental studies were made on the extremities of individuals immediately after death. Just preceding death, one of the extremities was raised so as to empty it of venous blood, and the other was lowered over the side of the bed, or was subjected to a pressure of 40 mm. Hg by means of a blood pressure cuff in order to maintain a full venous system. By this manipulation it was possible to study the influence of venous pressure on arterial flow.

Immediately post mortem, cannulae were placed in the femoral arteries and femoral veins, the arterial cannula being connected to an "artificial heart" or a heart-lung preparation (Fig. 1). Defibrinated animal blood was perfused through the extremity. The inflow of blood into the extremities was measured by means of a volume recorder in the case of the artificial heart, and a mercury gauge in the

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case of the heart-lung preparation. In each instance a pulsatile pressure was used in order to simulate the pressures produced by a normally beating heart. Observations were made both on normal extremities and on those in which there had been clinical evidence of peripheral vascular disease.

RESULTS

In normal legs whose veins had been emptied ante mortem, difficulty was encountered in forcing the blood into the arteries, even when the procedure was attempted immediately. In such cases it was necessary to place a tourniquet around the leg and to elevate the venous pressure from 10 to 20 mm. Hg to re-establish a maximum arterial inflow. In normal legs whose veins were distended before death, no difficulty was

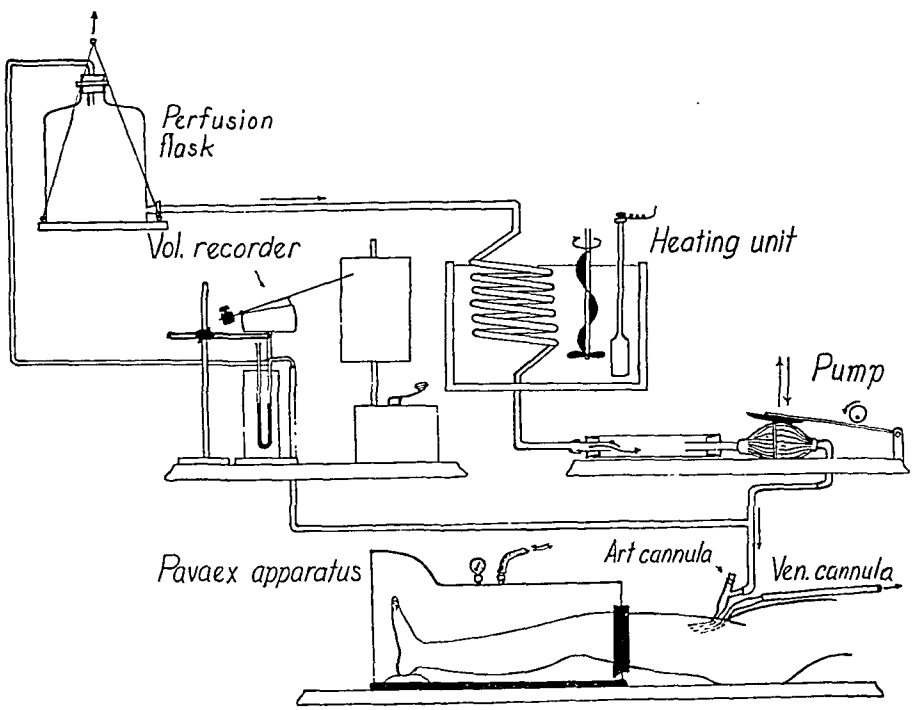

Fig. 1.—Diagram of the perfusion apparatus used.

encountered in passing blood through the extremity from the artery to the veins, unless sufficient time had elapsed after death to permit the blood to clot. The results for the normal extremity did not vary greatly from those established by other methods in man.[8] The extremities of individuals with clinical disease of the peripheral arteries were more difficult to study. In the first place, it was not possible to obtain a calculated arterial inflow. Under these circumstances the greatest possible inflow was utilized, and the factors determining it were evaluated. Since the maximum inflow varied with each extremity, it had to be established for each one. Considerable difficulty was then experienced until it was discovered that passing hypertonic saline (5 per cent)[9] through the vessels increased the blood flow immediately. It was found that when the perfusion of extremities of individuals with normal vascu-

lar trees was not begun until thirty or forty minutes after death, the difficulty was the same as that encountered when extremities with diseased arteries were perfused immediately after death. Only by passing hypertonic saline through the vessels could one obtain, or even approach, the normal calculated flow through the extremity. Since the only similarity between the two states was that the extremities had been deprived of oxygen, it was considered possible that the phenomenon was due to a reaction of degeneration. Increasing the arterial or venous pressure appeared not to influence the arterial rate of flow under these conditions.

It was assumed that the action of hypertonic saline in opening diseased vessels was attributable to dehydration of the capillary endothelium. Swelling of the capillary endothelial cells has been demonstrated as a reaction not only of degeneration, but at one time was suggested as a mechanism by which all capillaries were constricted.[10] These experiments suggest that an elevated venous pressure exerts a favorable influence on the passage of blood through the arteries. This important fact had been previously considered in the treatment of peripheral vascular disease by Silbert[16] and by Collens and Wilensky[11] and others.[15, 17] It appears that in partial arterial obstruction the veins or venules may collapse, thus offering further obstruction to an already enfeebled circulation. Increasing venous pressure by application of a tourniquet to the limb permits a backflow into collapsed venules, causing them to distend and enhancing the passage of blood through the arterioles and venules. One may liken this mechanism to a valve which can only be opened by elevating the venous pressure.

In six other experiments on the same extremities, after the maximum blood flow had been established, the pavaex apparatus was placed over the leg. Usually the arterial inflow as well as the venous output was diminished during the negative phase of the cycle. In three experiments the machine caused a definite decrease in the total blood flow during the time that the boot was on the extremity. There was some variation of inflow of blood to both the normal and diseased extremities. Immediately after the negative cycle began, there was usually a slight increase in the arterial inflow; whereas immediately after positive pressure was applied, the outflow from the venous side was increased.

Studies on the extremities begun immediately after death seemed to indicate that there are two definite factors to be considered in the treatment of peripheral vascular disease. One, and perhaps the most important, is that of increased venous pressure. The pavaex machine satisfies the factor to some extent when the negative phase of the cycle is removed. It must be emphasized, however, that a blood pressure cuff,[11] or a tourniquet can accomplish the same effect on venous pressure. A second important factor is dehydration of the vascular tree, presumably more especially of the capillary cells. Passage of hypertonic solu-

tions directly into the arteries in our experiments had a definite favorable influence on re-establishing the circulation, especially in diseased arteries.

CLINICAL OBSERVATIONS

The clinical material was divided into two groups. Twenty-five patients were treated primarily with the passive vascular exercise machine alone, and twenty-three others were treated according to the principles established by the experimental studies. The former were given no supplementary treatment except improvement of local and general hygienic conditions, and advice in all instances to discontinue the use of tobacco.[6] Patients treated with the passive vascular exercise machine were received from both clinic and private sources. In addition to the usual physical examination and laboratory tests (urinalysis, blood count, and Kahn test), some were examined roentgenologically after thorotrast injections in the vessels of the extremity; others had routine studies, such as skin temperature tests before and after treatment, and oscillometric readings of pulsation in the extremities, in addition to a careful vascular history.

Method of Treatment in First Group.—The passive vascular exercise unit devised by Herrmann and Reid and made by the Taylor Instrument Company[4] was usually employed, although the one devised by Landis and Gibbon[5] was used in three cases. The negative pressures usually varied from −60 to −120 mm. of mercury, while the positive pressure was +20 mm. of mercury. The machine was run at two or three cycles a minute. The cuffs at the top of the boot were those described by Herrmann and Reid. Some difficulty was always encountered in maintaining airtight connections and at the same time preventing obstruction to the venous return. In some cases special cuffs were used.

Most of the patients were hospitalized for a portion of the time. This applied especially to those with ulcers of the feet. All patients receiving the treatment were given careful instruction about care of the feet and advised to abstain from the use of tobacco. Buerger's exercises[12] were usually used to supplement the treatment. None of the patients, regardless of their economic condition, received supplementary treatment until after 20 hours of therapy. After that, biweekly administration of 100-300 c.c. of 3 to 5 per cent saline intravenously was begun and, unless contraindicated, intravenous typhoid vaccine was given to induce hyperpyrexia.

Arteriosclerosis (Table I).—Seventeen cases out of the total of twenty-five were diagnosed arteriosclerosis. Of this group, most patients received more than fifty hours of pavaex treatment, some as much as one hundred hours. Four patients were perhaps slightly benefited during the active period of treatment, since they were able to walk farther without pain in the extremity and also with less numbness and tingling. In no case, however, was there complete disappearance of symptoms, nor was there any notable change in the oscillometric reading of the extremity. In some instances thorotrast injections were made and showed obstruction of the arteries, usually of the femoral artery, before treatment. When this procedure was repeated after treatment, no evidence of increased anastomosis could be demonstrated. In Case 11 the ulcer of the toe healed during treatment. The patient was in the hospital for one and a half months and at the same time received the very best of care. He was a farmer, and his feet were dirty before

therapy began. The improvement of general hygiene appeared to be an important factor in the treatment. He is the only patient in the entire series who showed definite improvement following the therapy.

Thromboangiitis Obliterans.—Eight patients with thromboangiitis obliterans were treated, and in two there was improvement, as evidenced by the ability to walk from two to four blocks farther without pain and with definitely less numbness and tingling in the extremity. The remaining nine patients showed minor improvement. In no case of this group was ulceration of the feet or gangrene of the toes benefited. In two cases it was made so much worse that the patients refused to have the boot treatment and were discharged from the hospital and went to a second hospital where the therapy was advised, tried, and discontinued. In each case the leg was amputated.

One patient with embolic obstruction of the femoral artery was treated. Because of the extreme swelling which had persisted, only

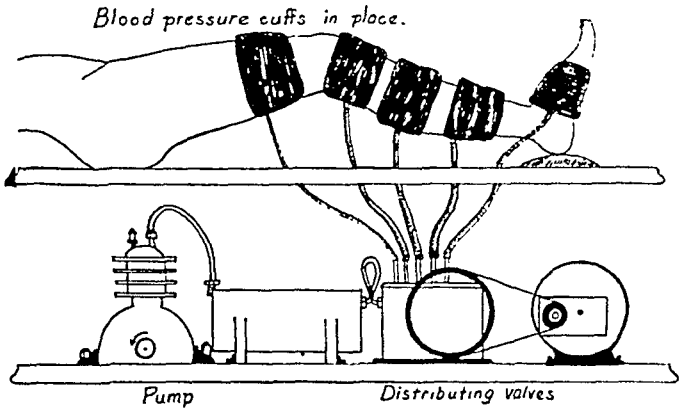

Fig. 2.—Diagram of the multiple blood-pressure cuff unit.

small pressure changes could be used and these did not effect any notable change in the extremity. The patient developed gangrene in spite of the therapy, which was then discontinued and a Sanders bed substituted, following the use of which the patient improved for a few days but died later from a cerebral embolus.

The results were very disappointing with any single method, especially with the pavaex machine. Our experimental studies had emphasized the apparent necessity for elevating the venous pressure in a diseased limb. To accomplish this, the following therapeutic measure was devised:

The treatment consisted of applying multiple (five) blood pressure cuffs to an extremity in order to maintain a high venous pressure. The pressure was about 40 mm. Hg for the cuff highest on the leg. Lesser pressures were applied to the succeeding cuffs, usually about 20 mm. Hg. The system was inflated and deflated every six minutes. The use of multiple cuffs appeared to shorten the total time that was necessary to maintain the venous pressure. We believe this was due to the fact that multiple cuffs tend to prevent distention of the superficial vessels of the

limb,[14] thus forcing the blood into the muscles and other deep tissues. The cuffs were usually applied two hours a day. Detailed reports of the machine will be made later.

Treatment of the Second Group.—This group (23 patients) was given treatment in which the venous pressure was elevated each day for two hours, as described above. Twice each week intravenous injections of 150 to 300 c.c. of 3 to 5 per cent saline solution were given, with due consideration for the general state of the individual's cardiovascular system. Intra-arterial injections have been avoided in arteriosclerosis where thrombi are expected because of the possible danger of breaking the thrombus free. The intra-arterial injections directed into the diseased artery in thromboangiitis obliterans appear to us to be more satisfactory than the intravenous saline injections. Hyperpyrexia, produced by the injection of typhoid vaccine, has been used in all our cases of thromboangiitis obliterans. The use of alcohol in the form of a highball before meals twice a day, in individuals with arteriosclerosis, has been substituted for fever therapy because of the relative danger of treating elderly patients with it, though in three of the younger patients with arteriosclerosis it was felt safe to use the vaccine.

Arteriosclerosis (Table II).—Twelve of the twenty-three patients were thought to have arteriosclerosis. All received about fifty hours of vascular congestion at the rate of two hours a day, five days a week. The effect of treatment in all of the individuals was to relieve pain and physical discomfort. It permitted those who were not otherwise handicapped to return to work, where they have remained for at least four months. There has been no tendency toward return of the symptoms to date. Two patients of the series could not be helped; any treatment caused severe pain in the extremity, accompanied by elevation in skin temperatures and greater volume of peripheral pulses.

Thromboangiitis Obliterans.—There were eleven cases of thromboangiitis obliterans. Each patient received from twenty to fifty hours of vascular congestion. The period of treatment was six months. The patient was instructed to discontinue tobacco in all forms.

The results obtained in this group of cases were most encouraging. Improvement began after the first week, and the capacity for normal physical activity returned within three months. Four patients stated that they had some numbness of the extremity throughout the five-month period. Three of the patients had rather severe ulceration of the feet which healed completely. All of them showed increase in pulsation of the peripheral arteries and often showed some increase in skin temperatures.

DISCUSSION

The great array of methods which have been devised to treat peripheral vascular disease indicates that each in itself may be insufficient. Recent reports and our own experience appear to place passive vascular

TABLE I

PATIENTS TREATED BY PASSIVE VASCULAR EXERCISE

CASE	AGE	TOTAL HOURS	DAYS	SYMPTOMS AND SIGNS BEFORE TREATMENT	COMMENT ON CONDITION AFTER TREATMENT
				Thromboangiitis Obliterans	
1	55	11	11	I.C.* after walking 2 blocks. Obstruction high in left leg. No pulse in feet.	Temporary improvement.
2	42	56	100	Painful gangrenous toe on right foot. No pulse in foot. I.C. at 2 blocks.	No change.
3	38	70	37	Pulse in both extremities poorly palpable. I.C. at 2 blocks.	No change.
4	50	51	40	Pain in foot at rest. Gangrene of 2 toes. No pulse. I.C. at ½ block.	Can walk 3 blocks without pain. Rest pain about the same as before.
5	44	21	15	Paresthesia present on left foot which was cold. Pulse fair. I.C. at 3 blocks.	No change.
6	47	45	38	Pain on standing or walking. Pulse fair.	No change.
7	50	48	90	Cold right foot. Ulcer on toe. No pulse. I.C. at 2 blocks.	Less pain for a few weeks. Leg amputated.
8	45	15	72	Paresthesia at times for 2 years. Pulse fair. I.C. at 3 blocks.	Less paresthesia. Very little improvement.
				Arteriosclerosis	
9	68	25	15	Patient was diabetic. Great toe previously amputated. Wound slow to heal.	Foot unimproved, later amputated.
10	60	45	12	Pain in right foot at all times for 3 months. No pulse in foot or popliteal artery.	No relief.
11	58	50	40	Pain at rest in both feet. Ulcer in left great toe. I.C. at 2 blocks.	Ulcer improved as result of cleanliness in hospital.
12	67	42	33	I.C. at ½ block. Paresthesia over both feet. No pulse in either foot.	Paresthesia less. I.C. at 4 blocks.
13	52	22	14	Pain in right foot. Popliteal pulse absent.	Color of skin improved. Pain somewhat diminished.
14	72	108	37	Pain at rest. Feet cold and cyanotic. No pulse.	Pain at rest less. No obvious improvement otherwise.
15	67	82	25	Pain at rest. Ulcer on left large toe. Foot cold. No pulse.	Pain at rest more severe. No change in ulcer.
16	62	75	40	Left foot cold. No pulse. I.C. at 2 blocks.	Can walk 2 blocks.
17	73	24	7	Pain and swelling in right foot for 4 weeks. Foot cyanotic, cold. No pulse.	No change. Pain persisted during treatment.
18	56	109	35	Night pain while at rest. No pulse in foot. I.C. at ½ block.	Slight temporary improvement. I.C. at 3 blocks. Night discomfort persistent.
19	67	65	66	Patient a diabetic. Pain in feet at rest. Pulse weak. I.C. at 6 blocks.	No definite change notable.
20	70	45	50	I.C. at 2 blocks. Paresthesia over dorsal and calf. No pulse. Feet cold.	Less pins and needles. No objective change. Able to work standing.
21	55	48	40	Ulcer on foot.	No improvement.
22	57	50	90	Pain with exercise.	No improvement.
23	61	36	45	Ulcer on foot. I.C.	No improvement.
24	67	14	6	Thrombosis of left popliteal.	Pain increased. Amputation.
25	80	30	14	Gangrene of left foot. Foot sloughed.	Pain less severe.

*I.C. is intermittent claudication.

TABLE II

PATIENTS WITH ARTERIOSCLEROSIS TREATED BY MULTIPLE CUFF METHOD

CASE	AGE	HOURS OF TREATMENT	DAYS	SYMPTOMS AND SIGNS BEFORE TREATMENT	AFTER TREATMENT	SALINE 3 PER CENT 100-300 C.C. INTRAVEN.	HYPERTHEMIA LOCAL OR IV. TYPH.
1	60	55	40	I.C.* No pulse in rt. ft. or poplit. art.	Pain imp. Pulses greater.	12	Local
2	58	48	52	Pain at rest, both feet. I.C. at 2 blocks.	Pain relieved. I.C. at 8 blocks.	12	8
3	67	52	80	I.C. at ½ block. No pulses both feet.	I. C. at 8 blocks. Pulses same.	15	8
4	52	38	40	Pain rt. ft. No pulses, either ft.	Pain in rt. ft. disappeared.	10	7
5	62	58	100	Pain at rest. Ft. cyanotic. I.C. after few steps. Ulcer lt. gt. toe.	I.C. at 4 blocks. Rest pain gone. Ulcer healed.	20	
6	56	51	60	Pain at rest, both feet. I.C. ½ block.	Sl. improvement. Relief of rest pain.	8	Local
7	67	37	66	Diabetic, rest pain. Pulses weak. I.C. at 6 blocks.	Improvement questionable. I.C. continued. Mentally confused. Unable to state clearly.	3	Local
8	70	33	45	I.C. at 2 blocks. Paresthesia over dorsum feet. No pulses.	Imp. No pain. Pulses present, but weak.	10	Local
9	55	52	90	Ulcer on lt. ft.	Ulcer healed. Cleanliness important factor in therapy.	7	Local
10	57	100	60	I.C. at 2 blocks.	Imp. I.C. at 20 blocks.	dilute 1%	5 Local
11	72	45	35	Pain. I.C.	Made worse. Block of nerves for relief of pain.	3	Local
12	64	140	70	I.C. at 2 blocks. Night pain, rt. leg. Numbness.	Improved. Relapse. Received therapy again with improvement.	12	10

*I.C. is intermittent claudication; *imp.*, improved; *rt.* and *lt.*, right and left; *ft.*, foot or feet.

exercise in this category. As Allen and Brown[7] have reported, it may help to relieve the pain in asthenic neuritis, but this has been rather rare in our series. Some of the patients have been relieved of pain while their legs were in the machine, or during the first weeks after treatment

began, but on the whole there has been little if any definite improvement, either in the pain associated with vascular disease or in increasing the blood supply.

Landis and Hitzrot[13] reported improvement in many of their patients with peripheral vascular disease, some of whom had diabetes, thrombo-

TABLE III

PATIENTS WITH THROMBOANGIITIS OBLITERANS TREATED BY MULTIPLE CUFF METHOD

CASE	AGE	HOURS OF TREATMENT	DAYS	SYMPTOMS SIGNS BEFORE TREATEMNT	AFTER TREATMENT*	SALINE 3 PER CENT 100-300 C.C. INTRAVEN.	HYPERTHERMIA LOCAL OR IV. TYPH.
1	55	54	60	I.C.† at 2 blocks. No pedal pulses.	Improvement. I.C. at 25 blocks.	20	8
2	42	48	36	Painful gangrene gt. toe rt. foot. I.C. at 2 blocks.	Healing. Lost I.C.	14	7
3	38	48	50	I.C. at 2 blocks. Rest pain.	Lost I.C. and rest pain.	10	6
4	50	28	40	Pain both feet. I.C. at 1 block. Cyanosis.	Improvement. Lost I.C.	10	6
5	44	35	30	Paresthesia, lt. ft. Pulses good.	Lost paresthesia. Improvement in walking.	8	3
6	47	42	55	Pain at night. Cyanosis.	Improved. Lost night pain.	12	6
7	42	42	55	Pain at night. Large ulcer, rt. ankle.	Leg finally amputated.		
8	45	50	40	I.C. at 3 blocks, redness and pain.	Improved, can walk 20 blocks. Comfortable.	12	6
9	27	48	84	I.C. redness, Cyan.	Loss of redness. Comfortable.	22	10
10	47	20	120	Pain and redness.	Imp. Loss of pain. Some numbness.	8	5
11	39	44	60	I.C. pain, redness.	Complete healing.	22	10

*"After treatment" includes time patient was under treatment and several weeks thereafter.

†*I.C.* is intermittent claudication; *imp.*, improved; *rt.* and *lt.*, right and left; *ft.*, foot or feet.

angiitis obliterans, and arteriosclerosis. They report relief of pain during the period of treatment with passive vascular exercise but do not record observations as to the permanent effects of the treatment on the pain. They were unable to convince themserves, however, that gangrenous or sloughing lesions improved with the treatment. Landis believed that intermittent claudication became milder and exercise tolerance was slightly but definitely increased. In our experience a certain

amount of increase in exercise tolerance was obtainable because of the training of the patient with the type of apparatus used. Especially was this notable in an individual who was frequently tested from week to week; but, when it was discontinued for a period of a month or so, usually the increased exercise tolerance would diminish to approach the usual state. Most of our improvements in the first series might have been the result of abstinence from tobacco. All of the patients were or had been heavy smokers. In a few patients, who could not resist the use of tobacco, one could tell whether they had been smoking or not by occurrence of severe pain in the calf. It is felt that very little benefit is derived from the use of the passive vascular exercise machine.

SUMMARY

Twenty-five patients with peripheral vascular disease were treated with passive vascular exercise. There were seventeen cases of arteriosclerosis, and eight of thromboangiitis obliterans. Only a small degree of improvement was noted in any group aside from what we attributed to other forms of therapy. It is believed, from experimental and clinical studies, that three principles should be observed in the treatment of arteriosclerosis and thromboangiitis obliterans: (1) maintenance of a high venous pressure; (2) dehydration of diseased capillaries in order that the blood may pass through them; and (3) when necessary, stimulation of the heart and arterial side by hyperpyrexia or by the milder methods.

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THE BLOOD PRESSURE RESPONSE TO EPINEPHRINE ADMINISTERED INTRAVENOUSLY TO SUBJECTS WITH NORMAL BLOOD PRESSURE AND TO PATIENTS WITH ESSENTIAL HYPERTENSION*

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EVER since Oliver and Schäfer[1] (1895) discovered that epinephrine has a pressor effect, the possibility that it may be a factor in hypertension has been considered. Many have tried to prove that the vasomotor mechanism in patients with hypertension is abnormally sensitive to epinephrine, or that excessive amounts of epinephrine are present in the blood of these patients. New evidence in support of the latter possibility has recently been brought forward by Kuré, Nakaya, Murakami, and Okinaka,[2] who maintain that atropine has a beneficial effect in hypertension. Hetényi and Sümegi[3] and Hess[4] have presented experimental evidence that the vasomotor mechanism in patients with hypertension is abnormally sensitive to epinephrine, but their results were not corroborated by Kylin,[5] Deicke and Hülse,[6] Jansen,[7] Gordon and Levitt,[8] and Pickering and Kissin.[9]

The observations of previous investigators were made following rather rapid intramuscular or intravenous injection of relatively small doses of epinephrine. It occurred to us that it would be interesting to compare the effects of more prolonged intravenous injections of epinephrine on the blood pressure and pulse rate of persons whose blood pressure was normal and patients with essential hypertension. The results which we obtained form the basis of this report.

PROCEDURE

Each subject was made to lie quietly on a couch for thirty to sixty minutes before the experiment was begun. The anterior cubital vein was then punctured, and physiologic salt solution was allowed to flow slowly into the vein. When the blood pressure, pulse rate, and cutaneous temperature of the digits had reached a stable level, the plain salt solution was replaced by a dilute solution of epinephrine hydrochloride in physiologic saline (1:250,000). The shift was accomplished by using two burettes, one containing plain salt solution, and the other the epinephrine solution, both of which were connected to the needle in the vein by means of a Y-tube. At intervals of two to five minutes, over a period of fifteen minutees, beginning at the moment when the subjective effect of the epinephrine was first noted, the systolic and diastolic pressures were measured, the pulse rate counted, and the cutaneous temperature of the volar surface of the distal phalanges of several of the fingers and toes taken. Temperature readings were made with Sheard's electromotive

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thermometer.[10] In some of the experiments a heat tent was placed over the subject's trunk forty-five to ninety minutes before the epinephrine injection was begun and was allowed to remain in position throughout the period of observation. The cold pressor test of Hines and Brown[11] was done on all of the patients with hypertension and on most of the normal subjects.

RESULTS

Experiments were performed on 12 persons whose blood pressure was normal and 10 patients with essential hypertension. The systolic pressure changes recorded represent the maximal increase above the resting level

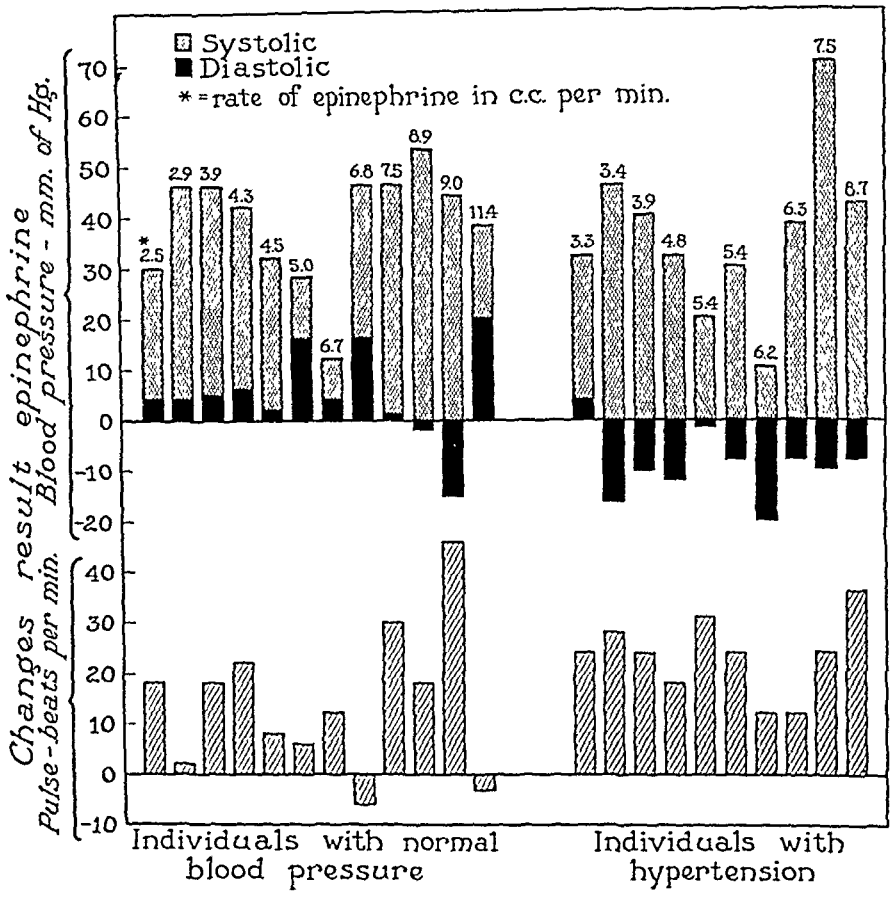

Fig. 1.—Graphic representation of response of blood pressure and pulse rate of normal subjects and patients with essential hypertension to intravenous injection, at varying rates, over fifteen minute periods, of dilute epinephrine solution (1:250,000).

during the fifteen-minute period, but, inasmuch as the diastolic pressures fluctuated both above and below the resting level, the changes recorded represent the maximal increase or decrease.

Tables I and II and Fig. 1 show that epinephrine had no more influence on the systolic blood pressure of patients with hypertension than on that of normal persons, that it usually lowered the diastolic pressure of patients with hypertension, and raised the diastolic pressure of the normal subjects. In the latter, the effect on the diastolic pressure was relatively less than on the systolic pressure. There was no visible cor-

TABLE I

Response of the blood pressure and pulse rate of subjects whose blood pressure was normal to intravenous injection, at varying rates, over periods of fifteen minutes, of dilute epinephrine solution (1:250,000); and the blood pressure response of the same subjects to the cold pressor test.

CASE	AGE, YEARS	BLOOD PRESSURE BEFORE EPINEPHRINE		BLOOD PRESSURE CHANGE; RESULT OF EPINEPHRINE		PULSE RATE		EPINEPHRINE INJECTION; RATE, C.C. PER MINUTE	BLOOD PRESSURE RESPONSE TO COLD TEST
		SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	BEFORE EPINEPHRINE	CHANGE; RESULT OF EPINEPHRINE		
1*	40	82	56	+30	+ 4	84	+18	2.5	80/60 to 100/ 70
2	23	114	78	+46	+ 4	76	+ 2	2.9	
3*	40	90	60	+46	+ 5	72	+18	3.9	100/60 to 110/ 75
4*	24	108	72	+42	+ 6	84	+24	4.3	90/65 to 105/ 80
5	42	110	72	+32	+ 2	84	+ 8	4.5	
6	35	112	68	+28	+16	66	+ 6	5.0	
7*	47	134	90	+12	+ 4	78	+12	6.7	120/80 to 155/100
8*	30	106	70	+46	+16	72	- 6	6.8	
9*	45	104	60	+46	+ 4 - 2	54	+30	7.5	90/50 to 108/ 60
10*	58	125	85	+53	+ 3 - 7	72	+18	8.9	90/65 to 145/100
11	33	126	65	+44	- 15	60	+46	9.0	110/65 to 142/ 90
12	48	98	56	+38	+20	90	-12 + 6	11.4	115/75 to 168/120

*Heat tent at 40 to 60°C. was placed over trunk forty-five to ninety minutes before injection of epinephrine was given. Tent was allowed to remain in position throughout the experiment.

TABLE II

Response of the blood pressure and pulse rate of patients with essential hypertension to intravenous injection, at varying rates, over periods of fifteen minutes, of dilute epinephrine solution (1:250,000); and the blood pressure response of the same patients to the cold pressor test.

CASE	AGE, YEARS	BLOOD PRESSURE BEFORE EPINEPHRINE		BLOOD PRESSURE CHANGE; RESULT OF EPINEPHRINE		PULSE RATE		EPINEPHRINE INJECTION; RATE, C.C. PER MINUTE	BLOOD PRESSURE RESPONSE TO COLD TEST
		SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	BEFORE EPINEPHRINE	CHANGE; RESULT OF EPINEPHRINE		
1	41	178	116	+32	+ 4	78	+24	3.3	170/120 to 235/155
2	28	152	88	+46	-16	84	+28	3.4	140/ 80 to 170/100
3	40	200	130	+40	-10	84	+24	3.9	195/130 to 230/150
4*	36	176	114	+32	-12	84	+18	4.8	190/120 to 260/150
5*	35	182	107	+20	+ 7 - 9	84	+31	5.4	170/130 to 230/145
6*	32	160	108	+30	- 8	84	+24	5.4	185/110 to 238/140
7	38	222	140	+10	-20	78	+12	6.2	180/140 to 250/165
8	46	190	118	+38	- 8	78	+12	6.3	190/120 to 230/130
9*	35	210	140	+70	-10	90	+24	7.5	200/130 to 250/170
10*	42	158	112	+42	- 8	84	+36	8.7	160/115 to 240/160

*Heat tent at 40 to 60°C. was placed over trunk forty-five to ninety minutes before injection of epinephrine was given. Tent was allowed to remain in position throughout the experiment.

relation between the systolic and diastolic pressure changes and the magnitude of the decrease in the surface temperature of the digits.

Although there was no correlation between the rate of injection of epinephrine and the blood pressure changes in the two groups as a whole, in individual instances the systolic pressure followed the rate so closely that it could be controlled fairly accurately by modifying the rate of injection. It is probable that much higher rates of injection would result in collapse,[12] with a corresponding fall in the systolic blood pressure. Blanching of the face proved to be a reliable sign of the onset of the epinephrine effect; the pallor persisted until the injection was discontinued, when it was succeeded by slight flushing of the face and neck.

It was observed that placing a heat tent (40 to 60° C.) over the trunk for forty-five to ninety minutes previous to the injection of epinephrine produced no appreciable fall in blood pressure, and that its presence during the injection did not influence appreciably the response of the blood pressure to epinephrine. There was no correlation between the blood pressure response to epinephrine and to the cold pressor test.

COMMENT

In showing that the systolic blood pressure of patients with essential hypertension is no more responsive to epinephrine than that of subjects whose blood pressure was normal, we have corroborated the results of previous investigators;[5-9] the fact that epinephrine, whether injected subcutaneously or intravenously, produces relatively little change in diastolic pressure has also been observed before.[13-16]

Bauer,[13] in 1912, attributed the rise in systolic pressure to increased cardiac activity, and the relatively slight rise, or decrease, in diastolic pressure to peripheral dilatation. The assumption that epinephrine produces vasodilatation in structures which contain a large proportion of the peripheral vascular bed is based on considerable experimental evidence. Vasodilatation occurs in the skeletal muscle of animals as a result of administration of epinephrine[12, 17, 18] except when large doses are given.[18-20] Furthermore, vasodilatation occurs in the splanchnic area, provided that the general blood pressure is raised; this dilatation is partly reflex and partly passive.[12] However, in the skin the action is uniformly one of vasoconstriction.[21]

The complex nature of the factors which determine changes of blood pressure in man as a result of the administration of epinephrine, together with the impossibility, from a practical standpoint, of analyzing these factors separately, makes it impossible at the present time to give an absolutely reliable explanation of the action of epinephrine on blood pressure. Bauer's assumption of increased cardiac activity and peripheral vasodilatation is probably the most satisfactory. In some of our experiments peripheral vasodilatation was induced by heat before the administration of epinephrine in order to facilitate demonstration of the

vasoconstrictor effect, but usually this procedure did not lower the diastolic pressure appreciably, and therefore nothing was learned concerning the effect of peripheral vascular tone on the response of the blood pressure to epinephrine.

Inasmuch as elevation of the diastolic blood pressure is a characteristic feature of essential hypertension, the fact that epinephrine usually produces a considerable increase in systolic pressure and a relatively slight increase, or even a decrease, in diastolic pressure may be taken as evidence that essential hypertension is not due to the presence of increased amounts of epinephrine in the blood. Likewise, the comparatively slight influence of epinephrine on the diastolic pressure indicates that the response to the cold pressor test is not an epinephrine effect, for, when the cold stimulus applied in the test raises the systolic pressure to a considerable extent, the diastolic pressure usually also increases markedly.

It has long been known that epinephrine causes constriction of the capillaries and arterioles of the skin,[22] and in our experiments, as well as those of Pickering and Kissin,[9] it invariably produced facial pallor. However, the facial color of most patients with essential hypertension is either normal or somewhat red, which is incompatible with the hypothesis that this disease is due to hyperepinephrinemia unless one assumes that the cutaneous capillaries of these patients are resistant to the action of epinephrine.

CONCLUSIONS

A dilute solution of epinephrine (1:250,000) was injected at varying rates, over a period of fifteen minutes, into the anterior cubital veins of 12 persons whose blood pressure was normal and 10 patients with essential hypertension. The results were as follows:

1. The magnitude of the rise in systolic pressure was the same in the two groups. In the patients with hypertension the diastolic pressure decreased more frequently than in the subjects whose blood pressure was normal. In both groups the change in diastolic pressure was always relatively less than the change in systolic pressure.

2. The induction of peripheral vasodilatation by applying radiant heat over the trunk did not appreciably alter the response of the blood pressure to epinephrine.

3. There was no evident correlation between the effect of the cold pressor test and epinephrine on the blood pressure.

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THE STETHOGRAPH*

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METHODS for recording heart sounds have been worked out by many investigators.[1-8] It is possible to review here only some of the outstanding contributions.

Einthoven and Geluk[9] (1894), using a stethoscope, carbon microphone, and capillary electrometer, were the first to make really satisfactory records. Later the string galvanometer was substituted for the capillary electrometer. Einthoven, Flohil and Battaerd[10] published the results of their work with the carbon microphone and string galvanometer in 1907. They suspended the microphone from the ceiling by three fine wires properly weighted for stability and connected it to the stethoscope through one arm of a Y-tube. The size of the opening in the other arm of the Y-tube was adjusted to remove apex impact vibrations. Their records were satisfactory, but the apapratus was complicated and its use restricted to the laboratory.

Wiggers[11] and Dean realized that Otto Frank's segmented capsule,[5] although fundamentally good in principle, had faults which seriously affected the quality of the sound records. They were primarily concerned with modifying the original Frank capsule so as to eliminate the low-pitched sounds caused by the "apex thrust." They also devised a capsule diaphragm with a sufficiently high natural period to record sounds of 100 to 150 cycles per second without distortion. Briefly, the Wiggers-Dean improvements of the Frank capsule consisted of (1) the use of a thinner and lighter membrane made of rubber cement, (2) the provision of a large side opening in the pickup tube to eliminate the low pitches of the apex thrust, and (3) the exclusion of extraneous noise by enclosing the capsule in a housing having a glass window. The method of Wiggers and Dean had an advantage over that of Einthoven in that it eliminated adventitious vibrations produced in the microphone.

Williams and Dodge[12] found that these adventitious vibrations were due to undamped motion of the carbon particles in the microphone Einthoven used. In 1920 Williams adapted an electromagnetic telephone to convert sound vibrations into electrical impulses. Because of its low initial sensitivity this method required an amplifier to obtain the necessary over-all amplification.

The stethograph† designed by the writer and introduced as the electrostethograph[13] is described in the following paragraphs. A schematic diagram of the instrument is shown in Fig. 1. It is made up of three main

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†Manufactured by the Cambridge Instrument Company as the Cambridge Stethograph.

components, namely, a microphone, an amplifier, and a recorder, and is contained in a single case weighing 22 pounds complete (Fig. 2). It operates on 110 volt alternating current.

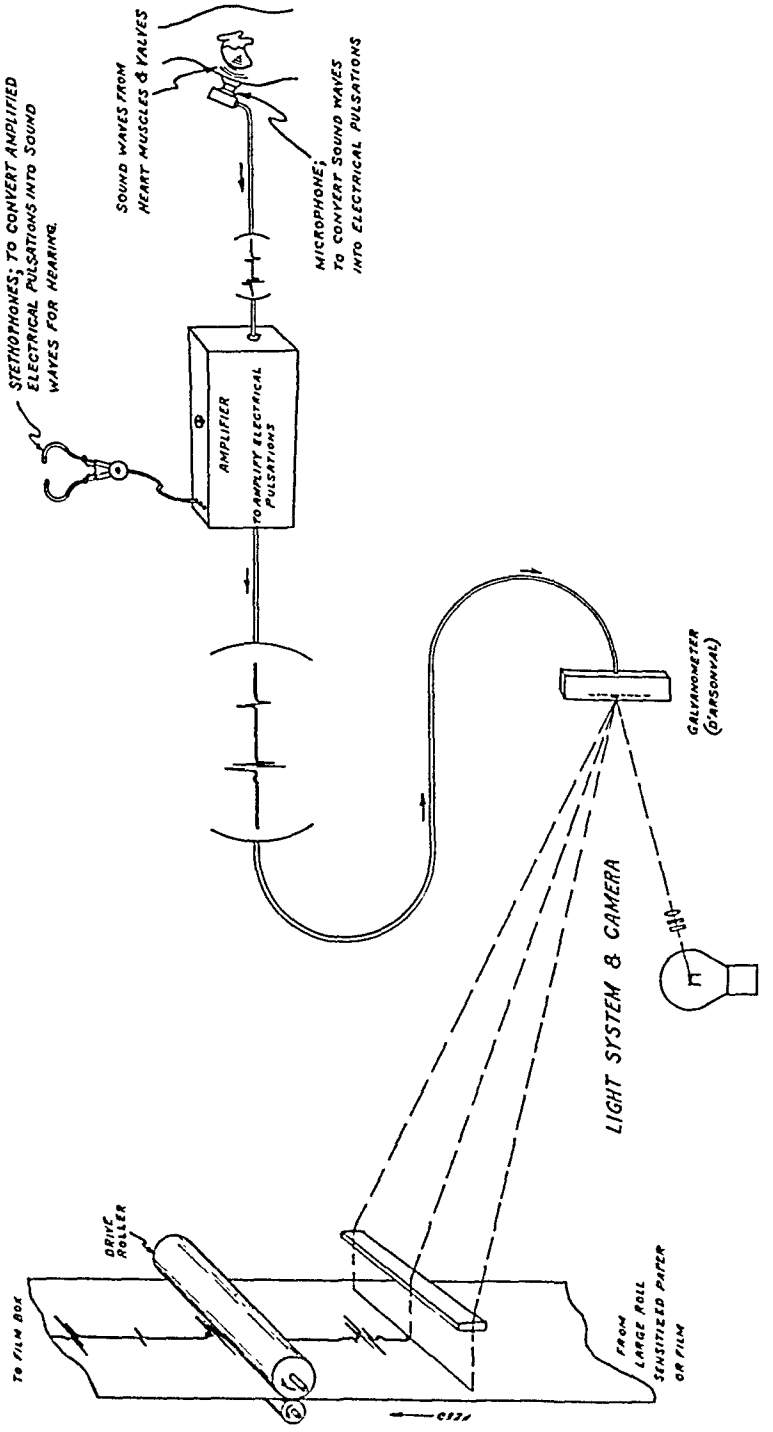

Fig. 1.—Schematic diagram of the stethograph. The sound waves produced by the patient's heart are picked up by specially designed microphone which converts sound pressure waves into electrical pulsations. The pulsations are amplified by a vacuum tube amplifier connected to a galvanometer. Stethophones reconvert the electrical pulsations, amplified many times, back into sound waves to which the ear is sensitive. The electrical pulsations flowing through the galvanometer produce oscillations of the galvanometer coil upon which a tiny mirror is mounted. Light falling on this mirror is reflected upon moving photographic paper.

The microphone is of the crystal type, and therefore free of inherent noises. The special crystal element is contained in a carefully designed case which provides an airtight housing for the crystal, eliminating the

effect of room noises. In addition, the shape of the interior is such that, when combined with the natural period of the crystal elements, resonance over a desirable frequency band is produced. Also, the necessary filtering (to be discussed later) is obtained acoustically in the microphone rather than electrically in the amplifier. The choice of the frequency band to be covered by the microphone was guided by the studies of Cabot and Dodge[14] and Williams and Dodge.[12]

The microphone provides an amplification increase of 300 per cent to 400 per cent within this desirable band, viz., 75 to 550 cycles per second

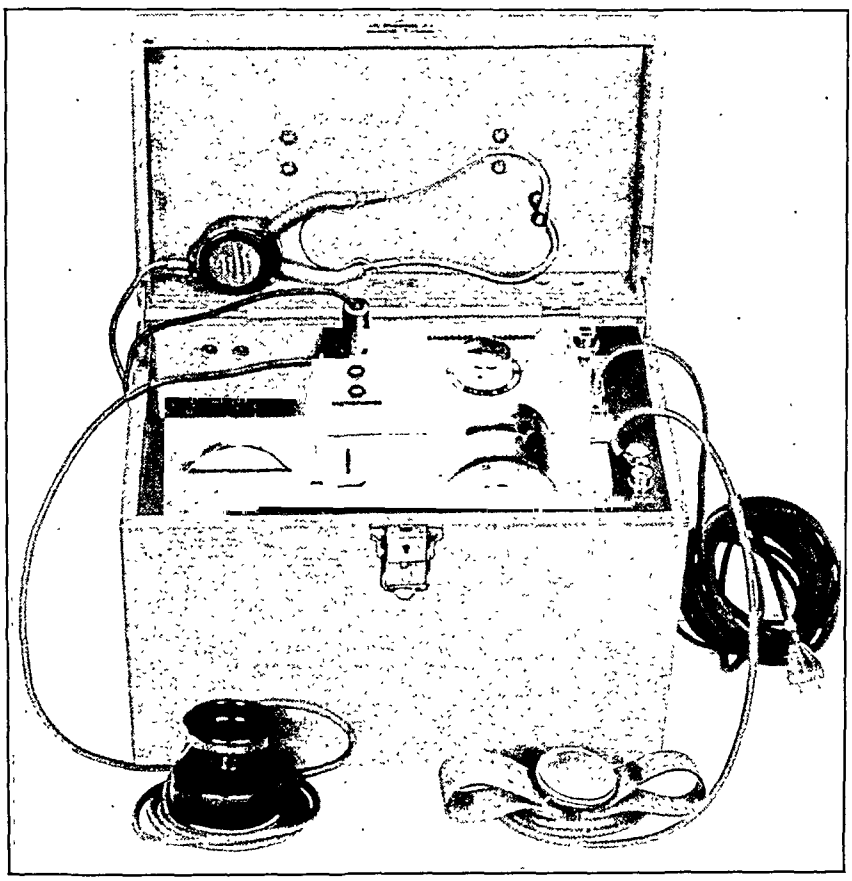

Fig. 2.—The Cambridge Stethograph (Courtesy of the Cambridge Instrument Co., New York).

(Fig. 3). The effects of room noises which are above this band are therefore greatly reduced. This accounts for the high "signal-to-noise ratio" obtained on the records. The effect is even more pronounced on the auditory senses because of the shape of the audibility curve of the human ear.[15, 16] "At the lower and upper limits of audition it takes about a hundred million times as much energy to enable one to hear as it does in the range of 1000 to 5000 cycles where the ear is most sensitive."[17] This characteristic of the human ear explains why the low-pitched murmur of mitral stenosis must become quite loud before it can be heard. It is sometimes easier to feel the apical thrill of mitral stenosis than it is to

hear the accompanying murmur because the sense of feeling is more acute than that of hearing in the portion of the frequency band occupied by this murmur.

A large amount of low-frequency energy is produced by the beating of the heart, most of which is caused by the striking of the apex against the anterior chest wall—the apex thrust. It is desirable to eliminate from the heart sound record all sounds which have no diagnostic importance. Those produced by the apex thrust are in this class, and the microphone was therefore designed to eliminate them. The cut-off and critical frequency points at the low-frequency end of the microphone response curve are important factors in the faithful recording of heart sounds, and the proper selection of these points determines the amount of diagnostic information furnished by the records.

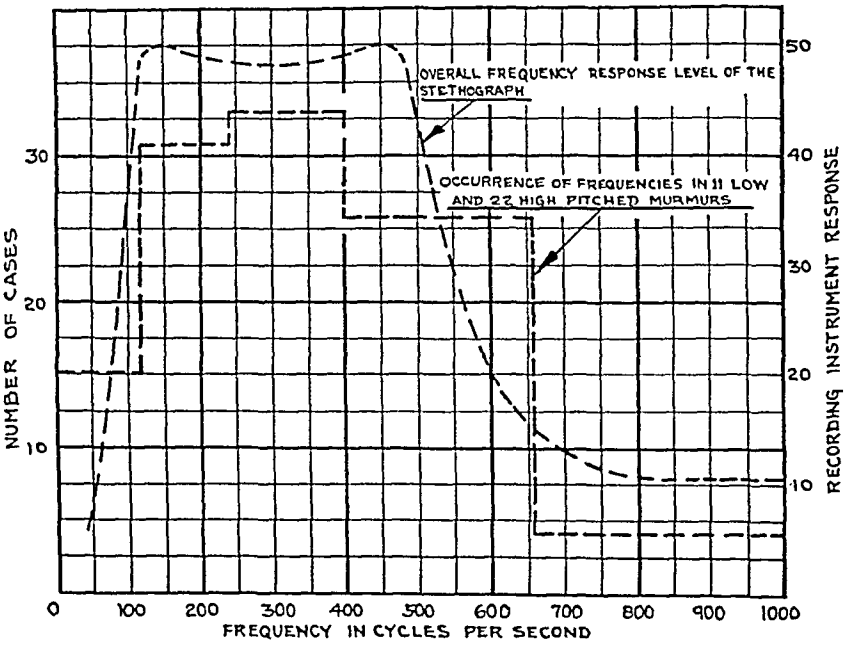

Fig. 3.—Comparison of the frequency band occupied by murmur sounds (as established by Williams and Dodge) with the response level of the stethograph.

The stethograph microphone is equipped with three bells which enable the operator to secure various degrees of filtering. The large open-faced bell shown with the microphone in Fig. 2 is called No. 1. The No. 2 bell is similar in size but is covered with a diaphragm. The No. 3 bell is approximately of the same size as that used on stethoscopes. The records shown in Fig. 4, all taken on the same patient, illustrate the effects of various degrees of filtering obtained by means of these bells. In record *A* there is a predominance of extremely low-pitched sounds, or "waviness," although at regular intervals greater excursions indicating the first and second heart sounds are evident. There are some high-pitched sounds within the systolic interval appearing as very small notches on the low-pitched ones. There is also a sound appearing regularly within

the systolic interval which, with the first and second sounds, simulates a gallop. There is another sound in the diastolic interval resembling a third heart sound. The predominance of the extremely low-pitched components in record *A*, however, makes it quite difficult to interpret.

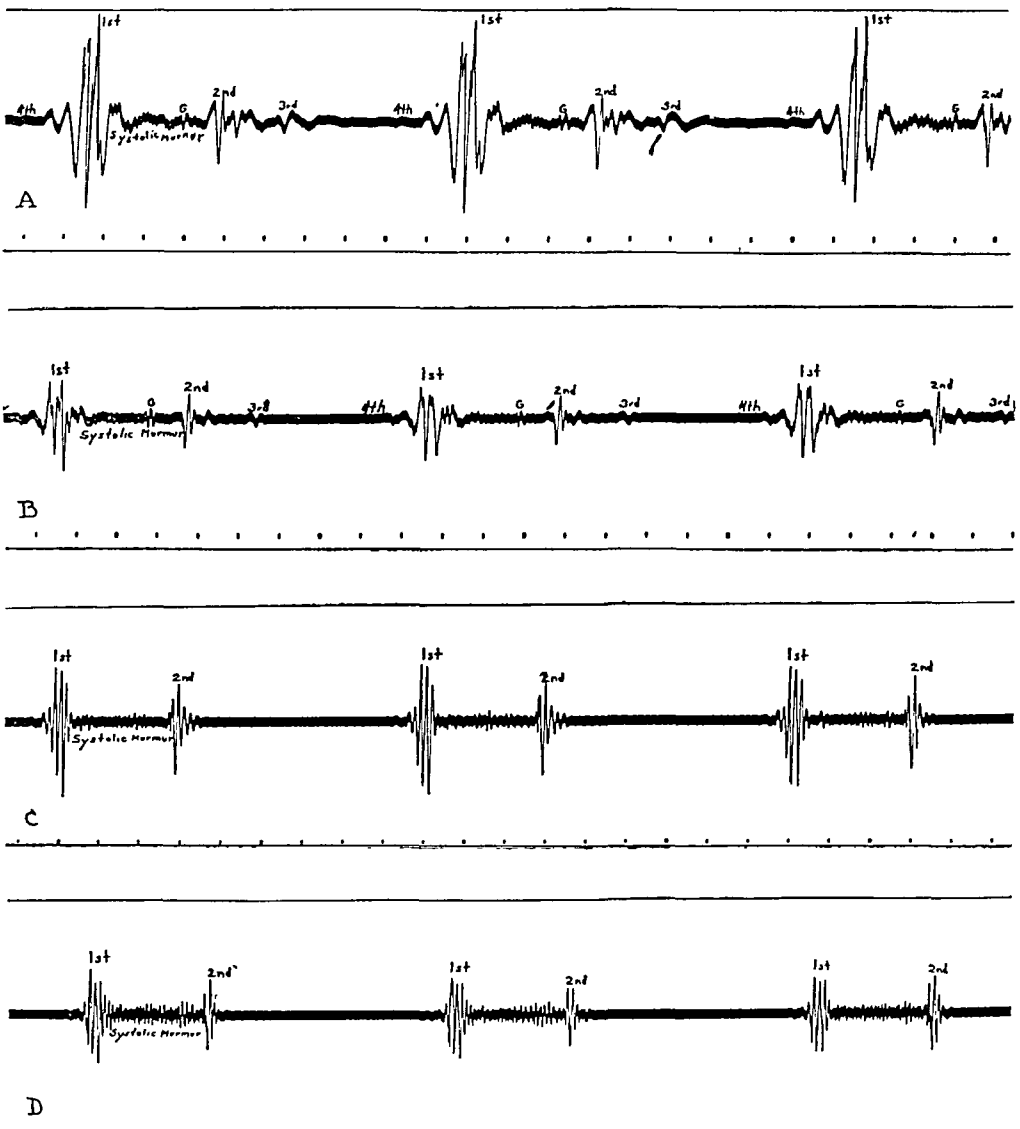

Fig. 4.—Effect of filtering heart sounds. The stethograph frequency response may be modified slightly by the use of three microphone bells supplied with the instrument.

A, taken with a special microphone, using the No. 1 bell. Very little low frequency filtering is provided by this microphone. The base line is too "wavy."

B, taken with the standard microphone using the No. 1 bell. Base line is now straight.

C, taken with the standard microphone using the No. 2 bell. Some important sounds are filtered out.

D, taken with the standard microphone using the No. 3 bell. Systolic murmur is magnified.

Record *B* illustrates the effect of a slight amount of filtering. Just enough of the low-pitched component has been removed to straighten the base line to a fair degree. The presence of a systolic murmur, the systolic gallop, and the third heart sound is now quite evident. There is

also a sound about 0.15 sec. ahead of the first sound, the auricular, or fourth, heart sound. Record *C* was taken with more filtering. The amplitude of the systolic murmur is increased in comparison with the first and second heart sounds. The base line is quite free from low-pitched components, but the systolic gallop, the third heart sound, and the auricular sound have disappeared. Record *D* shows the result of still more filtering. The systolic murmur has been artificially greatly increased in proportion to the first and second heart sounds, and, in the same manner, the low pitched sounds, as in the previous record, have been eliminated. On auscultation the systolic murmur was quite loud, but the systolic gallop, third heart sound, and auricular sounds were inaudible. The amount of low-pitched sound present in record *A* only impairs its diagnostic utility. Although the systolic murmur does not show so prominently in record *B* as it does in records *C* and *D*, other phenomena stand out more clearly. For these reasons the degree of filtering used in record *B* is more satisfactory from a clinical standpoint.

The second component of the stethograph is the amplifier. The frequency response of this unit is practically flat over the 50 to 1000 cycle band. Combining the microphone frequency characteristic with that of the amplifier gives the overall response curve shown in Fig. 3.

The third major part of the stethograph is the recorder. The chief requirements of a recorder for work of this kind are light weight, simplicity of construction, and stability. In addition to the need for accurate records, it is desirable that they be easy to interpret. This is facilitated by the choice of a proper base line width and by running the film at a suitable rate of speed. The optimum speed is dependent to a large extent upon the frequency of the sounds to be recorded. In the stethograph a speed of 75 mm. per second has been found to be most satisfactory.

In making records with the stethograph shown in Fig. 2, the microphone is placed over the patient's heart and the pulse pelotte on the wrist. The light beams from the galvanometer and pulse-recording mechanism fall upon a ground-glass screen as well as on the film, which makes it possible to view the heart sound vibrations and the pulse pressure variations while they are being recorded. The ability to see the sphygmogram while seeing and listening to the heart sounds is a valuable aid in timing certain murmurs and helps the physician to correlate his experience in auscultation with the sounds appearing on the record. Three stethophones (more by a special jack attachment) may be used at one time.

The value of the stethograph lies chiefly in greater accuracy of diagnosis and in the fact that it provides a permanent record which can be used to supplement or to replace the verbal or written description of auscultatory phenomena.

The recording of heart sounds has been accomplished, with varying degrees of success, by numerous investigators[18] over a period of many years, but the method has not come into general use chiefly because the reliable apparatus available could not be taken to the bedside. With the introduction of the stethograph, which is a simple, accurate, and portable instrument, this difficulty has been overcome. It is to be expected that its use will aid in the solution of many of the problems of cardiac disease.

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HEART SOUNDS IN NORMAL CHILDREN*

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GRAPHIC records of heart sounds have been made by various techniques for over seventy years, but it is only recently that practical clinical methods have been devised. Lockhart's paper[1] should be consulted for a review of methods and for reasons why the stethograph† which was employed in this study is the preferred instrument. It might be well to re-emphasize the fact that the value of the record obtained depends greatly upon the physical characteristics of the instrument used.

The stethograph records clearly vibrations below 600 cycles per second, but those of higher frequency are recorded in such low amplitude that they are difficult to read. The dominant frequencies of almost all heart sounds and murmurs are below 1000 cycles per second, and most of them do not exceed 600 cycles per second.[2, 3] The high-pitched elements heard by the ear constitute but a small part of the vibrations actually present. In this instrument there is an amplification of 300 per cent in the range below 600 cycles per second, and therefore the murmurs which are hardest to hear, namely, the low-pitched apical diastolic murmurs, are the ones said to be most clearly recorded.

Schwarzchild and Feltenstein's instrument,[4] although built on the same basic principles as the stethograph, is so designed as to introduce into the records approximately the same distortions which are produced in the human ear. The stethograph records the vibrations as they actually occur, rather than as they are heard.

Before beginning the study of heart sounds in children with rheumatic heart disease, it was necessary to establish standards for normal children, for only isolated reports of certain characteristics of heart sounds have appeared in the literature. Moreover, since the stethograph is just beginning to be generally used, an investigation of its range of applicability seemed desirable. So far, the only reports on the use of the stethograph are those of Martinez Cañas,[5, 6] and he did not study a large series of normal records.

Through the courtesy of the Board of Education of Ossining, New York, and the kindness of Dr. Marshall Wood, the school physician, we were able to make records of 105 normal children in the Ossining public schools. Since these were taken at the time of the annual medical examinations, the physical status of each child was known. In addition, each

*From Irvington House for Cardiac Children.
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†Manufactured by the Cambridge Instrument Company as the Cambridge Stethograph.

child was examined by the author, particularly with reference to cardiac size and auscultatory findings. A careful history was taken, with special attention to the possibility of rheumatic infection.

In making the stethographic records, the usual precautions were taken to eliminate extraneous sounds, such as room noises, breath sounds, and muscle sounds. However, since these records had to be made in the public school, a certain amount of noise was unavoidable. Whenever the extraneous noise was great enough to interfere with interpretation of the record, another tracing was made. Routinely, records were taken at the apex with the subject in the left lateral position, and also over the pulmonic and aortic areas with the subject in the sitting position and leaning forward slightly. It was found important to keep the children warm and comfortable in order to avoid extraneous noises due to muscle tension or shivering. The child was asked to take a deep breath, breathe out, and then to hold his breath in expiration while the record was made. Some of the children made such an effort not to breathe that muscle noise was introduced. With these the record was started in expiration and continued through one or two respiratory cycles. The microphone was held against the chest wall by means of a rubber strap. A microphone bell with an opening 2 inches in diameter was used. Even with this wide opening it was essential to have the bell in exactly the right position and applied as lightly as possible. It is well known how sharply diastolic murmurs are localized, and we have found this to be true of third heart sounds, also. The position of the microphone was checked by auscultation and by watching the vibrations on the screen of the machine. The same amplification was used in every instance.

TABLE I

DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND SEX

AGE	5	6	7	8	9	10	11	12	13	14	15	16	17	TOTAL
Girls	4	3	4	3	4	4	5	6	1	1	1	–	–	36
Boys	2	6	2	4	2	4	2	11	10	12	4	6	4	69

RESULTS

Table I gives the sex and age distribution of the children whose heart sounds were recorded in this study. Neither age nor sex made any difference in the kind of records obtained.

Rhythm.—Sinus arrhythmia was present in all cases. The intersphygmic intervals were greater with normal respiration than when the breath was held, but always amounted to at least 0.03 sec. In 4 per cent of the cases the variation was so great as to amount to sinus arrest. No other arrhythmias were noted.

Heart Sounds.—Records of heart sounds are difficult to analyze, principally because heart sounds are never pure musical notes having single frequencies but are mixtures of frequencies, i.e., noises. Therefore, when the rate of vibration of heart sounds or murmurs is mentioned in this paper the dominant frequency is meant.

There are, of course, wide individual variations in these records. Certain patterns stand out as normal (Fig. 1). The first and second sounds are always prominent. The first sound consists typically of a few vibra-

tions of about 80 to 150 cycles per second preceded by two or three vibrations of increasing intensity and pitch and followed by several vibrations decreasing in pitch and intensity. The second sound starts more abruptly, is frequently shorter and somewhat lower in pitch (70 to 130 cycles per second) and of the same or less intensity. It, too, decreases in pitch and intensity toward the end. Schwarzchild and Feltenstein's findings agree roughly with these, the discrepancies being due to the different instruments used.

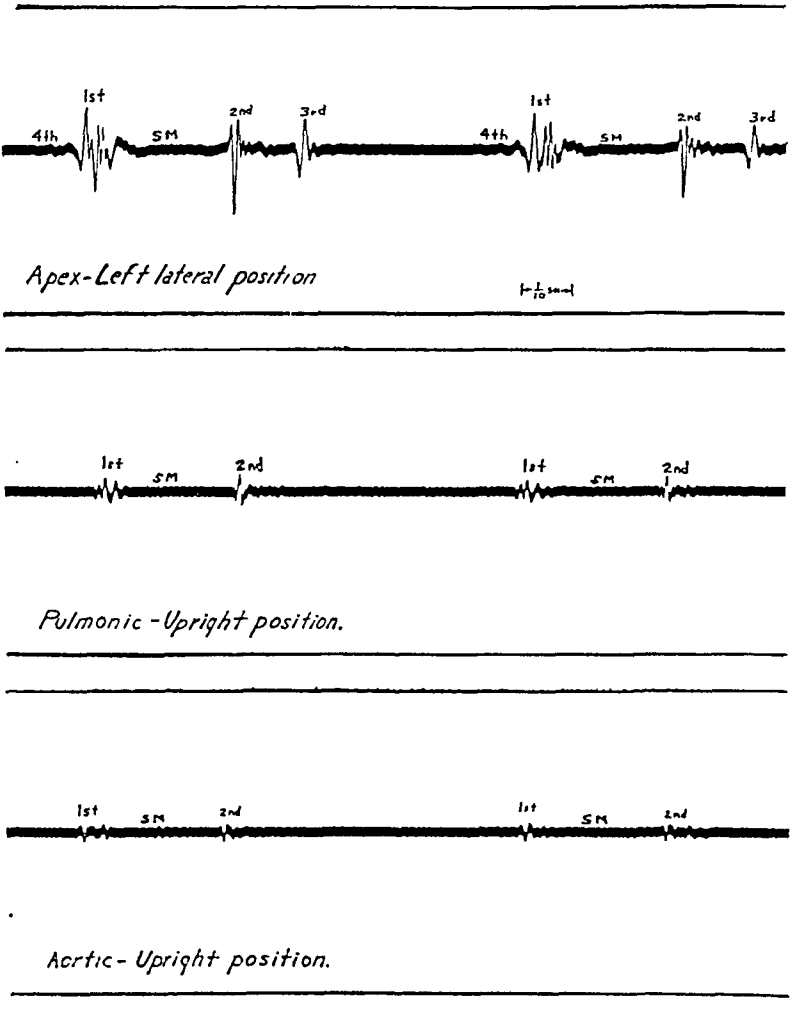

Fig. 1.—Normal heart sounds.

Only a separation of the sound into two distinct components was interpreted as true splitting (Fig. 2). In 24 cases (23 per cent) a split first sound was noted. In 38 cases (36 per cent) the second sound was split, and in 15 (14 per cent) of these both sounds were split. Split first sounds were recorded most clearly at the apex in 23 instances, the division in the other case being most distinct in the aortic region. In 8 cases the splitting was also visible in either the pulmonic or aortic tracing or both. Split second sounds were always clearest at the pulmonic

area and often distinct at the apex (25 cases). Siemsen[7] reports that in a group of normal boys ranging in age from 5 to 18 years split sounds were an almost constant finding. Cossio and Braun Menéndez,[8] in a group of 25 normal children from 5 to 10 years old, found two cases (8 per cent) of reduplication of the first sound and 12 cases (48 per cent) of reduplication of the second. Some clinicians regard a split second sound as suggestive of mitral stenosis, but its high incidence in normal children disproves this idea.

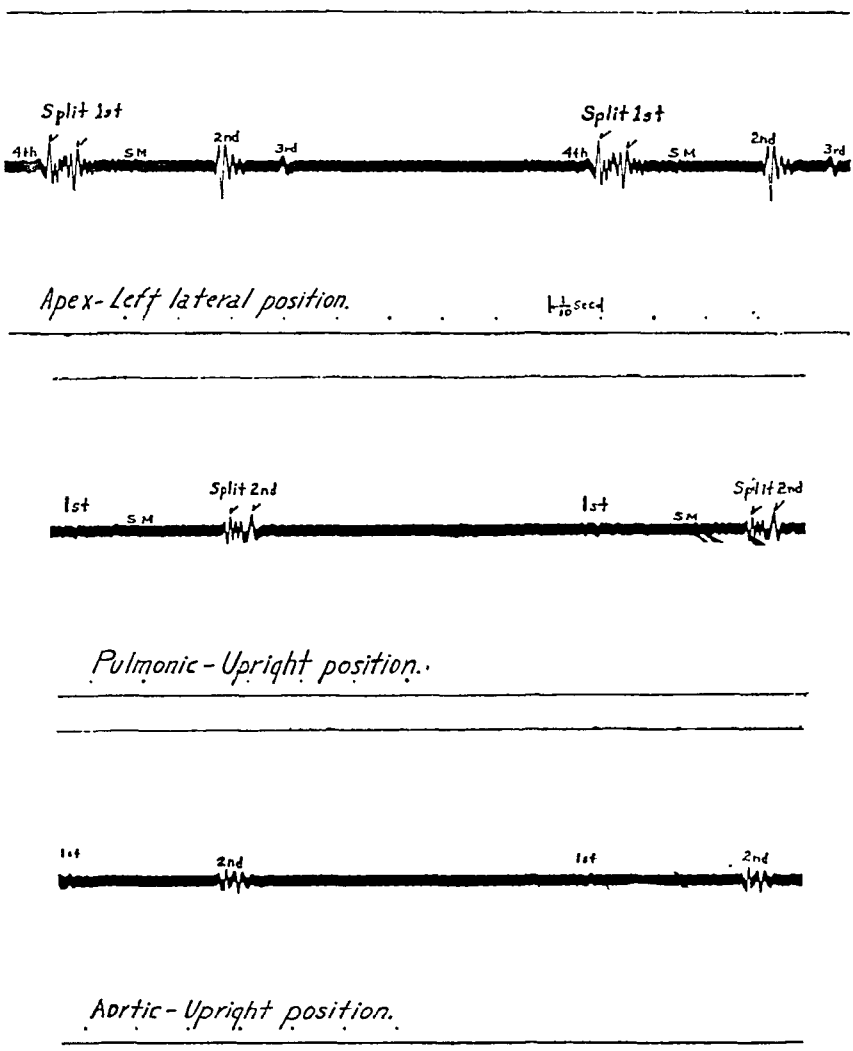

Fig. 2.—Normal heart sounds showing splitting of the first sound at the apex, and of the second at the base.

A third heart sound was audible in only 6 cases (6 per cent), but it appeared in the apex tracings of every child, being clearcut in 69 cases (66 per cent) and rudimentary in the rest. This third sound occurs from 0.11 to 0.15 sec. after the beginning of the second sound, always remaining at the same distance from the second sound in any single tracing. It is made up of one main vibration and sometimes one or more lesser vibrations of 20 to 50 cycles per second. The intensity of this

sound is quite variable; it is sometimes louder than the second (Fig. 3). Changes in rate occurring both during normal breathing and following exercise were studied carefully. Differences in cycle lengths were found to be due entirely to variations in the interval between the third sound and the following auricular sound (Fig. 4). The third heart sound is separated from the second by a constant interval which is not influenced by changes in heart rate due to exercise or respiration. Siemsen[7] found that 2 per cent of his group of school boys had third heart sounds in the upright position. Thayer[9] observed that the third heart sound is best heard when the patient lies on his left side. Braun Menéndez and Orias[10] recorded third heart sounds in 60 per cent of 100 medical students; Pereira[11] found that 32 per cent of a group of 50 normal pregnant women had third heart sounds in their phonocardiograms; and Segura[12] noted no third heart sounds in the records of 120 normal infants, but all of these studies were made with apparatus which is less sensitive to low pitches than the stethograph, which fact may well account for the lower incidence. Other observers (Wolferth and Margolies,[13] Braun Menéndez and Orias,[10] and Duchosal[14]) have noted that the physiologic third sound coincides with the final third of the V-wave of the phlebogram, that is, with the period of rapid filling of the ventricles. Some[15] think that it is caused by the opening of the mitral valve, and others[10] that it is due to vibrations of the walls of the ventricles set up by the sudden impact of blood from the auricles. In any event, it must be a physiologic phenomenon, for it is recorded by the stethograph in every normal child.

In 94 per cent of this group of normal children, the first sound at the apex was preceded by an interval of 0.05 to 0.10 sec. by another sound consisting of one, sometimes two, vibrations of 25 to 60 cycles per second, and of low intensity. The interval between these two sounds is soundless, showing that this earlier sound is not a presystolic murmur. Braun Menéndez and Orias,[10] in their series of medical students, report 20 per cent as showing auricular sounds preceding the first. In Pereira's work[11] with pregnant women, he found an incidence of about 17 per cent. Segura[12] noted a clear or vestigial auricular sound in 69 per cent of normal infants. His description of the sound is similar to that reported in this paper. In cases of heart block it becomes possible to show that auricular contraction is accompanied by a group of sounds composed of two sets of vibrations separated by a short interval.[6, 16, 17, 18] The second component, which occurs at the end of auricular systole, ordinarily forms the initial vibrations of the first sound, and is best transmitted to the precordium. The first component, which occurs at the height of auricular systole, is best transmitted to the esophagus. Both groups correspond in time to the early sound recorded in the stethograms of normal children. The interval between these two sounds of auricular origin does not correspond to the P-R interval; it may be the same, but

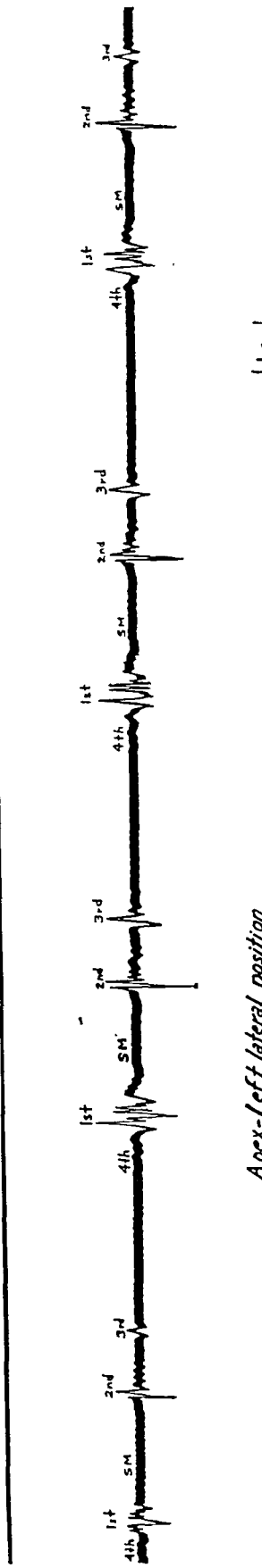

Fig. 3.—This record shows how respiration may alter the intensity of the various heart sounds.

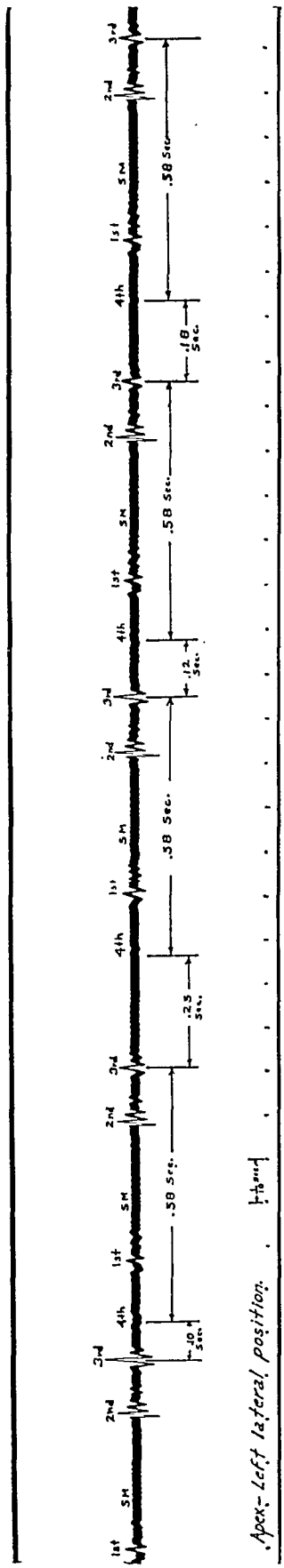

Fig. 4.—In this record, taken during respiration, the interval between the fourth, or auricular, sound and the succeeding third sound is constant (0.58 sec.), whereas the interval between the third and fourth sounds varies from 0.10 to 0.25 sec. The changes in the latter interval are due to sinus arrhythmia.

it is usually less. In seven cases in which electrocardiograms and stethograms were made simultaneously, the interval between the "auricular" and first sounds was less than the P-R interval in four cases, equal to it in one case, and slightly greater in two cases. The first component, which is synchronous with the height of auricular systole, has been attributed to vibrations of the ventricular wall due to expulsion of blood from the auricle,[10, 18] to vibrations of the auriculoventricular valves caused by auricular systole,[19] and to increased tension of the auricular wall and compression of blood in the auricular cavity.[16] The second component, which normally initiates the first sound, has been ascribed to ventricular distention,[10] to change of position of valve leaflets,[16] and to valvular distention.[19]

Variations in sounds.—The dominant frequencies of the various sounds tend to remain the same in each individual, regardless of the cardiac rate or of the sites at which the microphone is placed. The pattern of each sound tends to remain constant in successive tracings over the same area in the same individual, but to vary with change in site. The absolute and relative intensities of the sounds change greatly when the microphone is moved from one place to another and when the heart rate changes. The intensities of all the sounds vary in direct proportion to the heart rate. That of the first may increase as much as 900 per cent, the second 500 per cent, the third 800 per cent, and the fourth 1200 per cent (Fig. 4).

Systolic Murmurs.—Auscultation with the stethoscope showed that five of the 105 children had moderately loud systolic murmurs at the apex. They had no history suggestive of rheumatic infection, and no other signs of organic heart disease. In the stethographic records apical systolic murmurs were present in 90 per cent, and in most of the others the base line was so wavy that a systolic murmur may well have been present. In only one was the base line straight enough to rule out the possibility of a murmur. These murmurs have a frequency of about 120 cycles per second and are often transmitted to the pulmonic area. They follow the first sound, reach their maximal intensity early in systole, and gradually fade out, ending anywhere between the middle of systole and the beginning of the second sound. Those which are audible are similar to the others in appearance except for greater intensity. Table II shows the incidence (to ordinary auscultation) of functional systolic murmurs in other groups of normal children. No diastolic murmurs were observed in our series of normal children either by auscultation or in the stethograms. Thayer[9] suggests that the assumption of the left lateral position causes mitral insufficiency and accounts for the murmur. It is generally agreed that in children faint systolic murmurs at the apex are of questionable significance,[20-23, 9, 24] and our records indicate that such murmurs are not pathologic.

TABLE II

INCIDENCE OF FUNCTIONAL SYSTOLIC MURMURS AS DISCOVERED BY ORDINARY AUSCULTATION

AUTHOR	FIRST DECADE	SECOND DECADE
Lincoln[20]	8.3%	
Gibbes[21]	11.0%	10.7%
Thayer[9]	56.4%	35.7%

SUMMARY AND CONCLUSIONS

In order to establish normal standards, stethographic records were made on 105 apparently healthy school children. Four distinct sounds invariably accompanied each heart beat, namely, the first, the second, the "physiologic" third, and a supposedly auricular sound which preceded the first. The last two were low in pitch and usually of little intensity, and therefore are generally inaudible. The first or second sounds, or both, are frequently split.

Sinus arrythmia was always present. The differences in the intersphygmic intervals depend upon the time elapsing between the third sound and the following auricular sound. The intensities of the various sounds depend upon where the microphone is placed, and vary greatly with changes in the cardiac rate.

At the apex, a moderately low-pitched, usually faint systolic murmur was present in all instances, which suggests that too much significance should not be attached to such murmurs when they are barely audible with the stethoscope. No diastolic murmurs were encountered.

This investigation indicates that splitting of the first or second heart sound and the presence of a third sound have no pathologic significance.

The author wishes to thank Dr. Arthur C. DeGraff for his helpful suggestions throughout the course of this investigation.

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HEART SOUNDS AND MURMURS IN CHILDREN WITH RHEUMATIC HEART DISEASE*

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THE need of an objective method of studying heart sounds has long been felt. Observers differ as to the presence and timing of murmurs, and even the same observer varies in his ability to detect certain kinds of murmurs and sounds. The characteristics of some endocardial murmurs seem to change, and some even disappear from time to time. In such cases a means of recording heart sounds and murmurs would obviously be of great value. For this purpose we have chosen the stethograph† because it is accurate and easy to operate. The details of its construction will be found in Lockhart's paper.[1]

Normal standards were established by analyzing the stethograms of 105 apparently normal school children,[2] and this is a comparative study of 130 children with rheumatic heart disease. The subjects were 130 children between the ages of seven and sixteen years, all of whom had unequivocal histories of polyarthritis, chorea, or carditis of a rheumatic type. In each case the rheumatic infection was apparently quiescent at the time of admission. All but a few of the children remained at Irvington House from six to twelve months; records were made at intervals of approximately three months. As would be expected, some of the patients had recrudescences of rheumatic fever during their stay, and stethograms were made once or twice a week in nine of these cases. Altogether, more than 500 satisfactory records were obtained.

The technique was the same as that used in making the records on normal children; tracings were taken with the patient lying on his left side and the microphone over the apex, and from the aortic and pulmonic areas with the patient sitting up.[2]

RESULTS

Table I shows the distribution of these patients according to age, sex, and degree of cardiac damage as determined by clinical and roentgenologic examination.

*From Irvington House for Cardiac Children.
Received for publication March 3, 1938.

†Manufactured by the Cambridge Instrument Company as the Cambridge stethograph.

TABLE I

DIAG.	POSS. AND POT.		M I		M I (?S)		M I AND S		I AND S AI		M I AND S AI AND S	
AGE (YR.)	F	M	F	M	F	M	F	M	F	M	F	M
7			1					1				
8			2	3	2		6	2				
9	1	1	5	4		1	2	9		1		2
10	1	2	4		1		4	2		3		
11	1		2	3			5	4	3	1		
12	1	1	7	2	2		4	5	2	1		
13	3			1		1	4	1	2	1		1
14			1				4	2		1		
15							1	1		1		
16												1
	7	4	22	13	5	2	30	27	7	9		4

Poss. & Pot. = possible and potential.
M = mitral. A = aortic.
I = insufficiency. S = stenosis.

The records taken during the inactive phase of the disease will be described first. The criteria of the New York Heart Association[3] form the basis for the classification of these patients.

Rhythm.—Sinus arrhythmia was always present, as in normal children and was of the same degree. The cycle lengths varied in each record by at least 0.03 sec.

Possible and Potential Heart Disease.—(*E* and *F*, Fig. 1.) These 11 patients had all had rheumatic fever. All had systolic murmurs at the apex on auscultation, but no cardiac enlargement clinically or roentgenologically, and thus fell into the group classified by the New York Heart Association as possible and potential cardiac subjects. In the stethographic records, the heart sounds were like those of normal children in respect to pitch, intensity, and duration. The systolic murmurs were similar to those found in normal records in regard to pitch and length but tended to be of about the same amplitude as the normal ones which can be heard with the stethoscope. One record showed, following the third sound, a few small vibrations whose frequency was about 80 cycles per second. No diastolic murmur was ever heard with the stethoscope in this case.

Mitral Insufficiency.—(Fig. 2.) The New York Heart Association criteria for this diagnosis are enlargement of the heart and a systolic murmur at the apex. The 35 children in this group presented roentgenologic evidence of slight or moderate cardiac enlargement, and all of them had an easily audible apical systolic murmur which was "blowing" in quality. Thirteen of them had, in addition, an inconstant, short, faint, early diastolic murmur localized at the apex. These patients were included in this group because the latter murmur was inconstant, and there was no evidence of left auricular enlargement. In five of the stethographic records the second sound at the pulmonic area was disproportionately intense, which corresponds to "accentuation" in ordinary auscultation. Otherwise the heart sounds were all similar in shape to those in the normal series, that is, they follow the first sound, reach

their maximal intensity early in systole, and fade out toward the end of systole. These murmurs are of about the same intensity as the normal ones but are higher in pitch, reaching 150 to 200 cycles per second. One child's records showed a crescendo murmur which was also crescendo to auscultation. Thirty patients (86 per cent) had diastolic murmurs which followed the third heart sound, gradually faded out within the first half of diastole when the patients were at rest, were of low intensity,

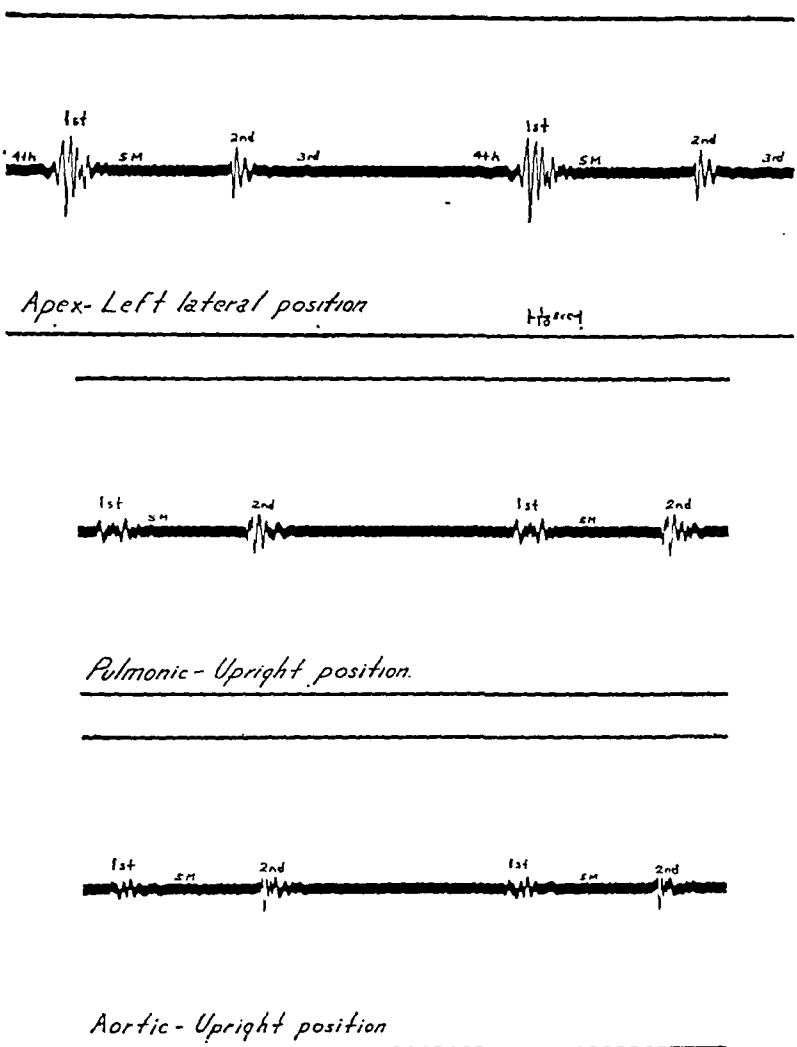

Fig. 1.—Heart sounds of a patient with potential and possible heart disease, having a history of rheumatic fever, and clinically showing a systolic murmur as the only possible evidence of cardiac damage. The record is like that of a normal heart.

and had a frequency of about 80 cycles per second. In ten of these thirty cases, records taken at different times showed sometimes a diastolic murmur and sometimes a third heart sound. The murmur even came and went with respiration (Fig. 3).

Mitral Insufficiency and Questionable Mitral Stenosis.—This group of six includes patients of two types: (1) those with cardiac enlargement, an apical systolic murmur, and a short, faint, early, apical diastolic murmur not rumbling in character, and (2) those with an apical systolic

murmur and a rumbling apical diastolic murmur, but without clinical or roentgenologic evidence of cardiac enlargement. Stethographic records in these cases showed systolic murmurs with the same characteristics as those of the preceding group. The diastolic murmurs were also like those of the preceding group except that one of them extended to the auricular sound.

Mitral Insufficiency and Stenosis.—(Fig. 4.) The criteria for this diagnosis, according to the New York Heart Association, are an apical systolic murmur, an apical diastolic murmur, and cardiac enlargement.

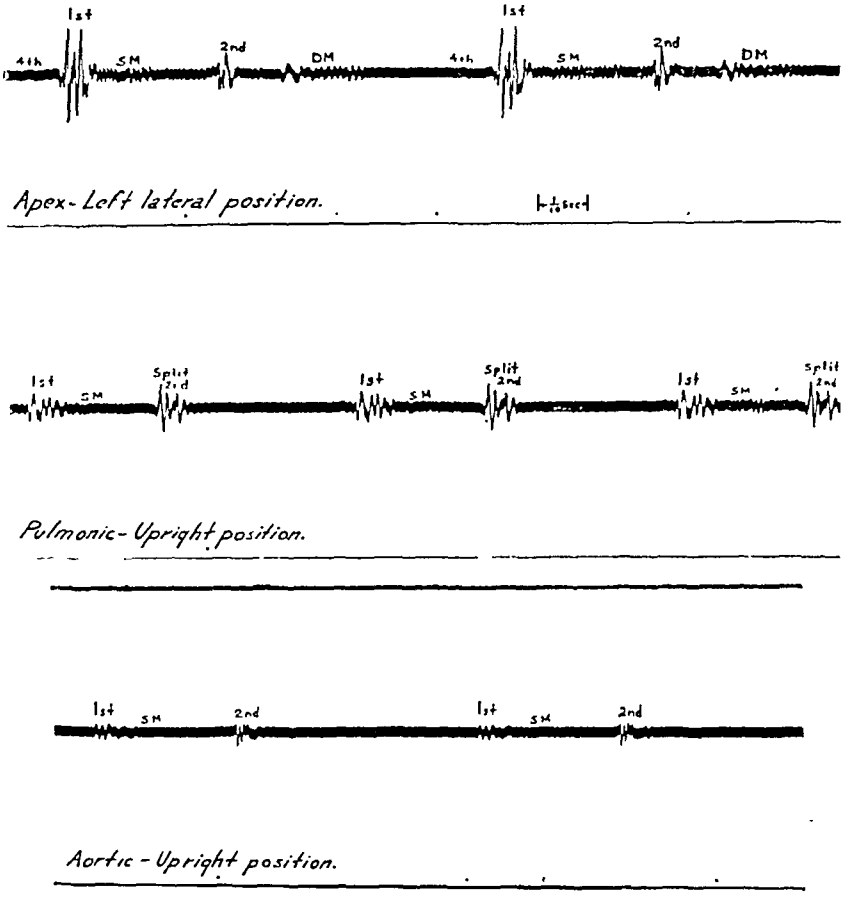

Fig. 2.—Heart sounds in mitral insufficiency. This patient gave a history of rheumatic fever and clinically showed cardiac enlargement, apical systolic murmur, and an inconstant early faint apical diastolic murmur.

By these standards the patients said to have mitral insufficiency and questionable mitral stenosis and some of those said to have simply mitral insufficiency should be included here. However, in this group of 57 only those with an apical systolic murmur, an at least moderately loud, persistent apical diastolic murmur, and definite cardiac enlargement are included. In the stethographic records eight (14 per cent) showed greatly accentuated second sounds at the pulmonic area. The systolic murmurs were similar to those described before, but of greater intensity, six (10 per cent) being as loud as or louder than the first sound. There was great

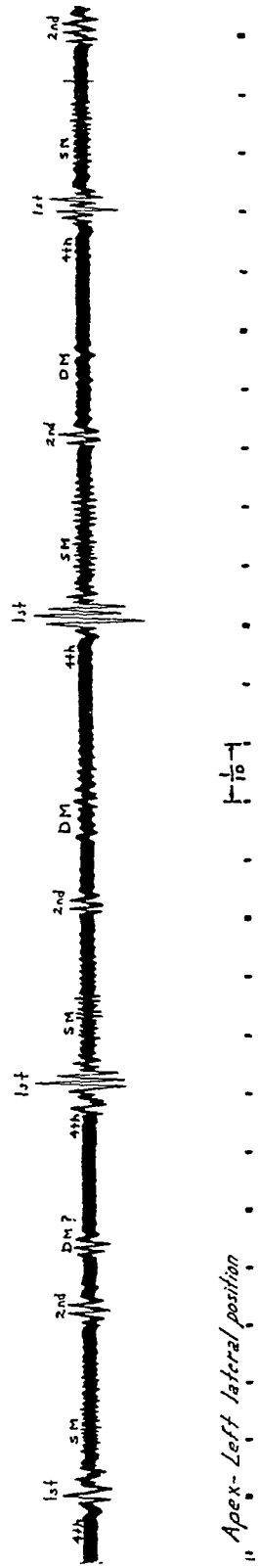

Fig. 3.—Heart sounds in mitral insufficiency. This patient had a history of rheumatic fever and clinically showed cardiac enlargement, an apical systolic murmur, and an inconstant apical diastolic murmur. This record taken at cardiac apex during a respiratory cycle shows the variation possible during this time.

variability in the diastolic murmurs. Some were like those described above, but others were louder than the first and second sounds and lasted throughout diastole. The frequency of the vibrations varied greatly, but was mainly less than 120 cycles a second. Three of these loud, long diastolic murmurs showed a presystolic increase in intensity (Fig. 5). In twelve other cases (21 per cent) the interval between the auricular and first sounds was occupied by a few vibrations of about 100 cycles per second, of increasing intensity. This is apparently the presystolic murmur which is often considered of great importance in the diagnosis of mitral disease. It is to be remembered that these records were all taken with the patient at rest. Had the patients exercised immediately

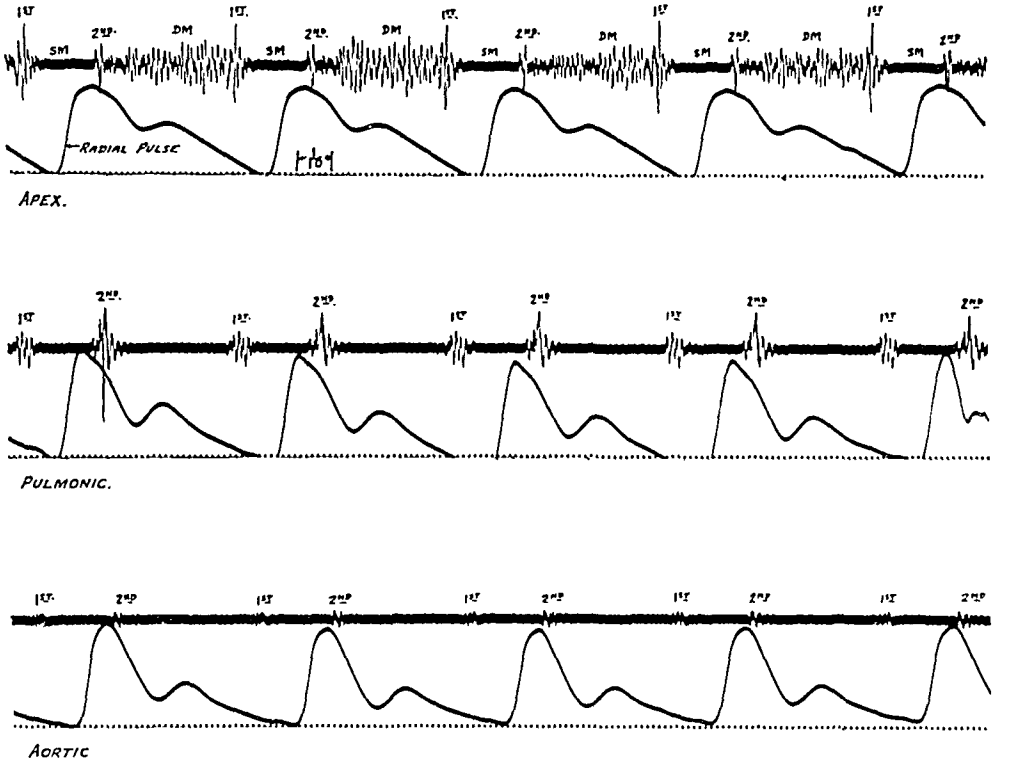

Fig. 4.—Heart sounds in well-established mitral stenosis and insufficiency. This patient had a history of rheumatic fever and clinically showed marked cardiac enlargement, a marked diastolic thrill at the apex, an apical systolic murmur, and a loud long rough apical diastolic murmur. Note the relatively quiet interval following the second sound.

before the records were made, it is possible the incidence of these murmurs would have been greater. *In these records the characteristic murmur was a low-pitched sound beginning at the time of the third heart sound and continuing a variable time into diastole.* There was always a relatively, though not absolutely, soundless interval between the second and third sounds.

Mitral Insufficiency and Stenosis and Aortic Insufficiency.—(Fig. 6.) The diagnostic criteria were the same as for the mitral lesions, plus a diastolic murmur at the base. There were sixteen patients in this group.

The stethographic records made from the cardiac apex were similar to those in the preceding group. Records taken with the microphone over the base of the heart show a diastolic murmur which begins immediately after the second sound, continues a variable distance into diastole, and is very low in intensity and comparatively high in pitch (180 to 240 cycles per second). Although these murmurs are easily audible with the stethoscope, they are difficult to distinguish in stethograms because of their low intensity. The reason for this difficulty lies in the fact

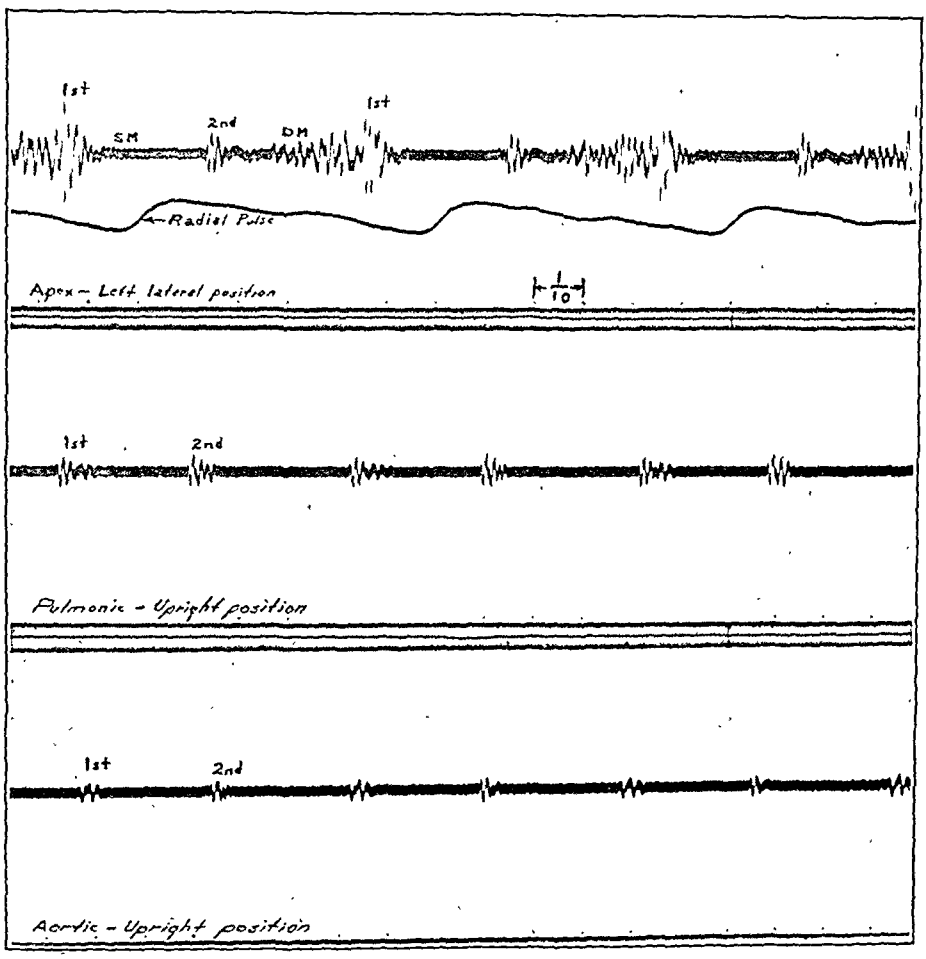

Fig. 5.—Heart sounds in mitral stenosis and insufficiency. This patient had a history of rheumatic fever and clinically showed moderate cardiac enlargement, a diastolic thrill at the apex, an apical systolic murmur, and a long loud rough diastolic murmur. Note the presystolic accentuation.

that of two sounds of the same intensity but of different pitch one will sound louder than the other to the human ear. A further discussion of this point will be found in Lockhart's paper.[1]

Mitral Insufficiency and Stenosis and Aortic Insufficiency and Stenosis.—In this group of four patients the diagnostic criteria were the same as for double mitral lesions, plus a diastolic blow and a rough systolic murmur at the base. The records were like those in the preceding group, with an additional systolic murmur at the base which was composed of a

mixture of frequencies, the most prominent being about 80 cycles per second. These murmurs begin immediately following the first sound and last throughout systole.

Active Carditis.—(Fig. 7.) Stethographic records in nine cases during periods of rheumatic activity were made at weekly or semiweekly intervals. When there was clinical evidence of carditis, sinus arrhythmia was less marked, and in three cases (33 per cent) was absent in at least two records.

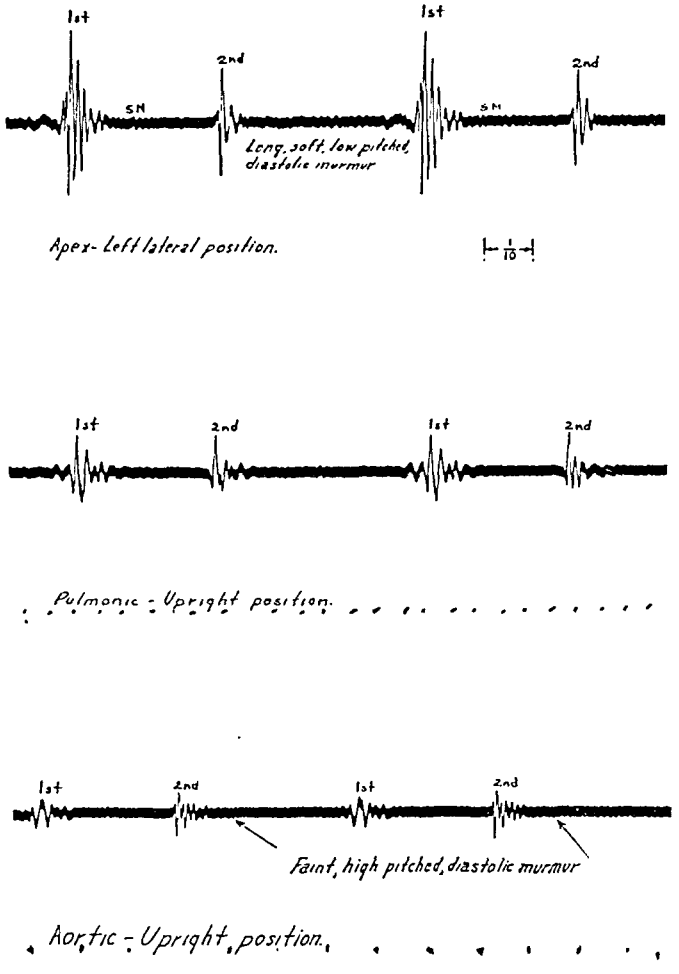

Fig. 6.—Heart sounds in mitral insufficiency and stenosis and aortic insufficiency. This patient had a history of rheumatism and clinically showed cardiac enlargement, apical systolic and diastolic murmurs, and a diastolic blow at the base.

This may be explained largely by the fast heart rate which accompanies carditis. However, the rate in stethograms showing absolutely regular rhythm was somewhat slower than that in several records in which sinus arrhythmia was present. Periods previously silent are no longer so for several reasons. It was noted in the tracings of normal children that changes in cardiac rate affected only the time interval between the third and auricular sounds. The tachycardia associated with rheumatic activity is similarly at the expense of the quiet part of diastole. There

is also an increase in the length and intensity of murmurs already present. Moreover, new murmurs often appear at this time. The murmurs which appear in these records do not differ from those seen when the rheumatic process is inactive. Clinically, the heart sounds are said to be of "poor" or "valvular" quality, but this difference does not stand out in stethograms. However, in three (33 per cent) the first sound decreased in amplitude, though remaining within the range of normal. This change takes place in the low-pitched components. The sounds are as long as normal ones. When a diastolic murmur of moderate intensity appears, the third sound is frequently lost. If the murmur disappears

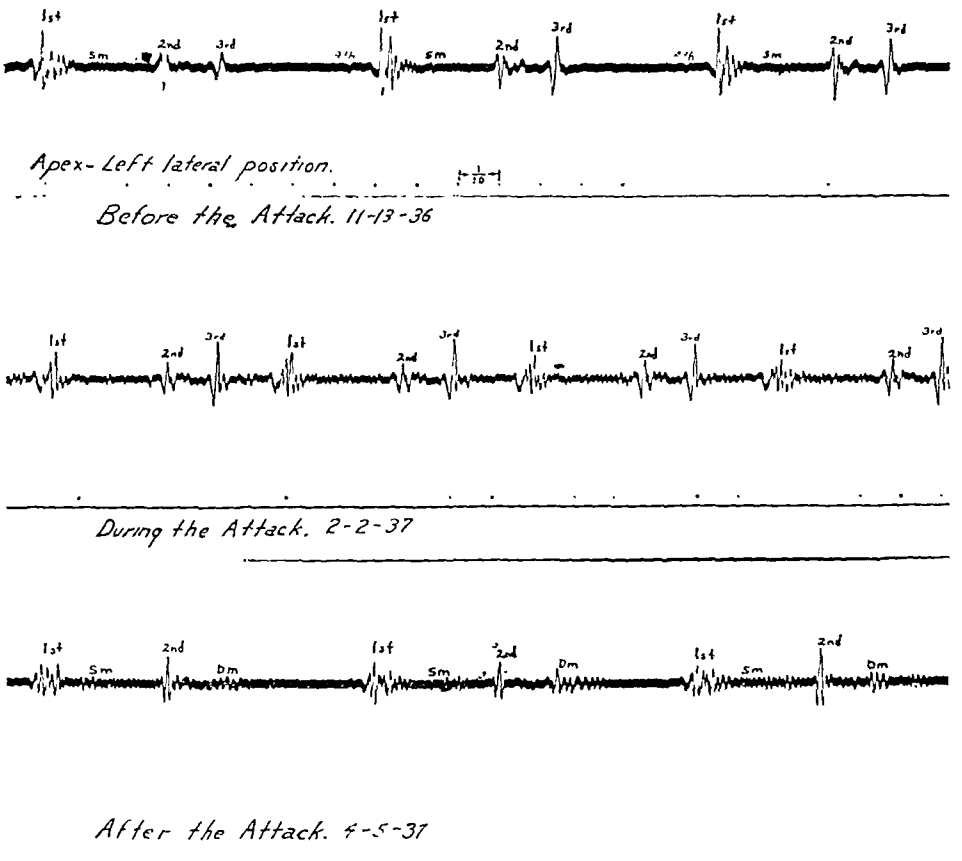

Fig. 7.—These records were taken at the cardiac apex of the same patient. The first was taken before, the second during, and the third following an attack of rheumatic fever. At the time of the second record the patient was considered to have gallop rhythm.

or becomes much fainter with recovery, the third sound reappears. During frank rheumatic activity the fourth sound was increased in amplitude, though still well within normal limits, in two cases (22 per cent). Gallop rhythm was noted with the stethoscope in three cases. The stethograms of these patients (Fig. 7) at this time showed a prominent third heart sound, although its intensity was not greater than in normal children. There was also a first sound of somewhat less than average intensity, but still well within normal limits. These sounds probably represent the gallop rhythm heard with the stethoscope.[4]

The small number of cases of active carditis included in this study, and the lack of consistency in the appearance of the stethograms preclude any statement as to the value of such records in the diagnosis of active carditis. However, a definite change in the appearance of the record might suggest the presence of carditis.

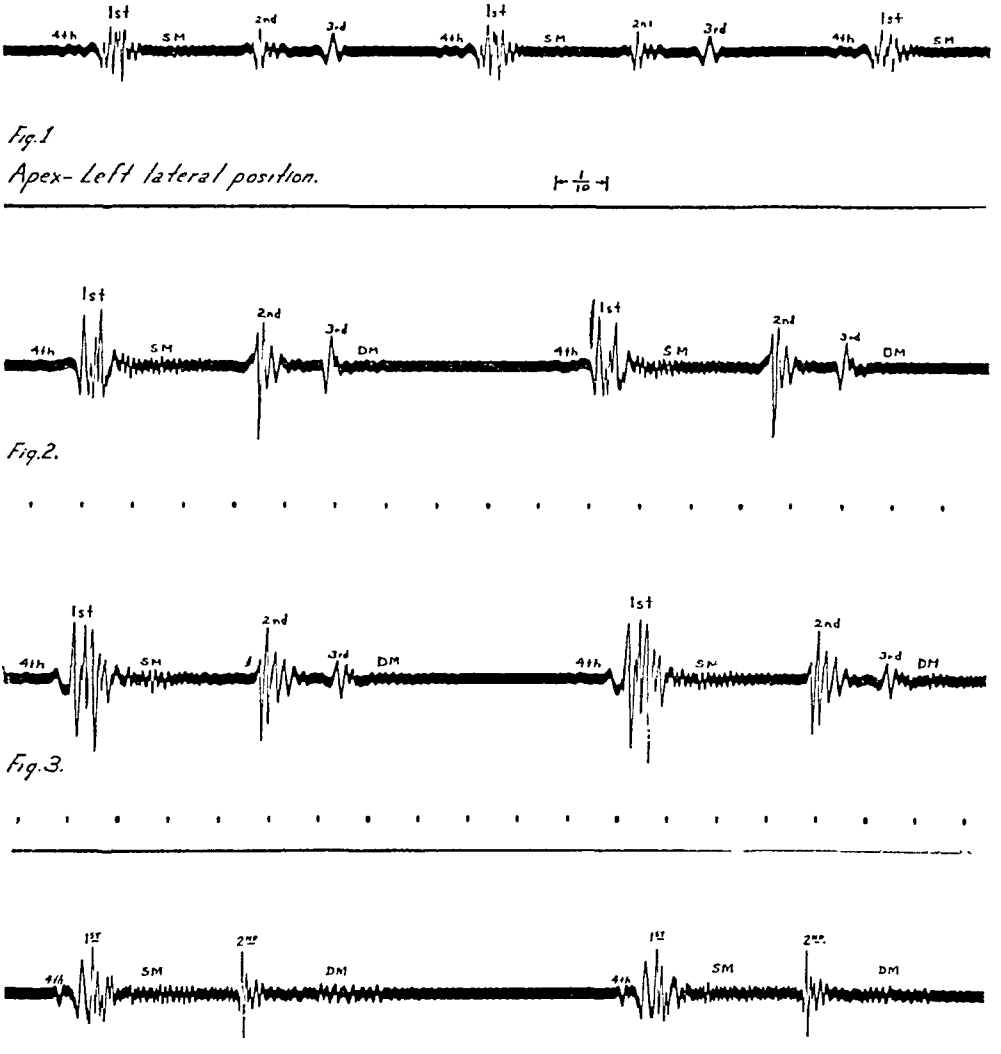

Fig. 8.—This series of records taken at the cardiac apex of four patients shows gradations between a third heart sound and a frank diastolic murmur.

DISCUSSION AND CONCLUSIONS

Stethograms of children with quiescent rheumatic heart disease show the same degree of sinus arrhythmia as those of normal children. In carditis this arrhythmia may disappear. Gallop rhythm may be due, at

least in some cases, to tachycardia, accentuation of the third heart sound, and lessening of the intensity of the first heart sound.

Nineteen per cent of 119 children with organic heart disease had abnormally loud second sounds at the pulmonic area. Otherwise the heart sounds were not outside the normal range.

The apical systolic murmurs which were present in cases of mild cardiac damage appeared similar to those found in normal records except for increased intensity. With more advanced heart disease these murmurs became slightly higher pitched.

The differences in the apical diastolic murmurs were interesting. On the whole, as would be expected, the louder, longer murmurs occur in cases in which the heart disease is relatively severe. However, when the disease is not so far advanced the short, early, faint diastolic murmur may come and go from time to time during periods of apparent inactivity of the disease. Stethograms of these children show sometimes a murmur and sometimes a third heart sound. The murmur may even come and go with respiration. Moreover, there are all gradations from a simple clear-cut third heart sound, such as is present in the stethogram of every normal child, to an obvious long diastolic rumble (Fig. 8). It is evident that there are adequate objective grounds in such cases for the disagreement of different observers concerning the presence of a diastolic murmur. This last series of records brings up the question of what should be called a murmur and what only a sound. In this work we have arbitrarily used the term murmur to designate any series of waves composed of more than three vibrations.

The significance of inconstant, faint, early diastolic murmurs has been widely debated.[5, 6, 7] It is possible that they may be due to slight relative stenosis of the mitral valve caused by cardiectasis without enlargement of the mitral orifice. Do such murmurs ultimately disappear, or are they the earliest sign of mitral stenosis? If stethographic records can be made in such cases at intervals over a period of years this question may be answered.

The author wishes to thank Dr. Arthur C. DeGraff for his helpful suggestions throughout the course of this investigation.

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Special Article

FIRST INTERNATIONAL HEALTH BROADCAST

7:30-8:00 P.M., MAY 2, 1938

Opening Announcement (Haddon Hall Hotel, Atlantic City):

This evening the National Broadcasting Company brings you the First International Health Broadcast. This program, conceived by a committee of Irvington House, Sanatorium for Children with Rheumatic Heart Disease, and presented under the auspices of the American Heart Association, is designed to stimulate greater public interest and action in one of the major child health problems—that of heart disease. The speakers on this evening's program, who will be heard from London, San Francisco, and Atlantic City, will be introduced by Dr. Howard W. Haggard, Professor of Applied Physiology at Yale University.

Dr. Howard W. Haggard, Commentator:

You are about to take part in an event unique in radio broadcasting. This is a pioneer venture—the first international medical consultation on a topic of grave significance to every man, woman, and child.

There are a few fortunate individuals who, in matters of health, may obtain the aid of famous physicians, but none could ever have such a consultation as is presented for you in your home tonight. This broadcast brings together men of pre-eminent authority from cities as distant as San Francisco, Boston, New York, and London. Representing on this occasion the medical profession of Great Britain is Lord Horder, the Physician-in-Ordinary to His Majesty King George VI.

The subject upon which these physicians will speak is "Heart Disease in Children." Its importance to you lies in the fact that today heart disease—a consequence of rheumatic fever—takes a greater toll of health and life, and destroys more children of school age, than any other ailment.

The discoveries of medical research, the efforts of our physicians, the enlightenment of our public, have worked together to free us from many of the once major mortalities of early life. We have seen the "choleras" of infancy wiped out and the diphtheria of childhood; we have seen the tuberculosis of adolescence brought under control. But the crippling rheumatic fever has not yet yielded, and it will not yield except before a united effort—the concerted determination to rid ourselves of it.

Tonight great medical authorities will define for you the situation that confronts us; they will tell what has been done and what can be done. Their words will be a call for you to enlist in a warfare of humanitarianism, a warfare against a disease that knows no national boundaries.

This call for your support to protect our children—and their children—by ending this disease is sponsored by the American Heart Association of New York City. This first international health broadcast was arranged by its Committee on Radio Publicity headed by Dr. Arthur C. De Graff, who is medical director of Irvington House, sanatorium for the care of children suffering with heart disease.

It is my great privilege now to present to you as the first speaker, Lord Horder, President of the Medical Society of London, Chairman of the Empire Rheumatism Council, and Physician-in-Ordinary to the King of England.

Lord Thomas Jeeves Horder:

Greetings to America, sturdy warrior in all campaigns against disease, the real enemy of humanity. The world's greatest monument to the triumphs of medical research is the Panama Canal, which your engineers were able to build only by first abolishing tropical disease in this area. May you do as good work against rheumatic disease, which is today Public Danger No. 1 of civilized mankind.

In our country rheumatic disease is the greatest of the killers, though it conceals its murders under the mask of heart disease. On the evidence of trustworthy statistics, we find that it is as it is with you: Organic disease of the heart is chiefly rheumatic in origin, and organic heart disease is the cause of over one-third of our annual death rate. One does not need to be a doctor to know of the number of heart cripples that are strewn throughout the community as the result of rheumatic inflammation during childhood.

How are we to grapple with this enemy? First by research to discover the causative factors. Then by diligent efforts in the field of preventive medicine to build up effective barriers against the operation of those factors. By such methods medical science has won splendid results in combating other scourges of man—bubonic plague, malaria, and typhus fever. I am confident it can be as successful with rheumatic heart disease.

Research to determine definitely the causes of rheumatism is the first essential. The prevention of disease is the ideal of modern medical science, and measures of prevention must be based on precise knowledge of causes.

This task of research into causes of rheumatic disease is a vast undertaking. It must, to quote a famous philosopher, "take all knowledge

for its province." It must investigate methodically, patiently, and with all precaution against mistake, every possible factor in causation. It cannot afford to base its policy on any single preconceived idea to the neglect of other fields of exploration.

We have much evidence here, as you have in America, that the type of rheumatism which affects the heart is closely associated with bacterial infection. It will surely not be long before we clarify this association.

But there must not be ignored what I shall call the sociologic factors, the influence of environment and possibly, also, of heredity. I have recently had the opportunity to study the figures of the incidence of acute rheumatic disease among a group of 30,000 youths, gathered into certain training institutions. All of them had been carefully examined and passed as first-class lives within the previous twelve months. Much the greater proportion of this group of youths were drawn from the poorer classes of the community. The incidence of acute rheumatism among them in a year was nearly five per thousand, and of other forms of rheumatism over seven per thousand. Of the sufferers, two died and seventy were permanently invalided. But in the much smaller proportion of this group of youths, drawn from the well-to-do classes, the cases of acute rheumatism and of other forms of rheumatism were so infrequent as to be almost negligible. From the same figures it could be seen that there was a similar relative incidence of such allied diseases as tonsillitis and acute ear trouble among youths drawn from different classes of the community. There is a clear hint, here, of a sociologic factor in the causation of rheumatic disease. Accepting, as I say I think we may accept, the fact that acute rheumatism is an infectious disease, the suggestion comes that some circumstances of early environment make the child's body a more favorable soil in which that infection can flourish.

But suggestions are not certainties. We must have certainty and, in the quest of certainty, we must follow up all the clues that offer themselves. So our investigations must be not only at the bedside of the patient and at the benches of the laboratory; they must explore conditions of climate, of diet, of housing, of occupation, to arrive at final conclusions.

The British Empire Rheumatism Council, of which I am chairman, has entered upon the task of exploring this wide field in the search for the causative factors of rheumatic disease generally. We shall have a complete clinical and research unit working specially on this problem of rheumatic heart disease. The Council will work in cooperation with your scientists and those of other nations. In particular it welcomes the prospect of having a close alliance in its work with the United States. Your people have won world-wide renown for the great measure of scientific skill and of philanthropic support which you have brought

to the effort of winning for man the fullest possible span of life and of a life healthy, vigorous and free from disablement. Rheumatic diseases are responsible, in our community, and probably also in your community, for one-sixth of the total illness; they cause more suffering and more death than cancer and tuberculosis combined; and they are notably cruel in their attacks on youth, wrecking life at its threshold.

A splendid vision can engage the minds of men if they will be wise enough to see the futility of fratricidal strife and recognize that their true enemies are the forces of disease—the vision of a world from which all preventable illness has been banished; in which sickness will come only as the penalty of wickedness or of folly. It is that vision which engages our attention just as it is engaging yours.

Dr. Howard W. Haggard, Commentator:

You have just heard Lord Horder of England, the opening speaker in this, the first international health broadcast which is sponsored by the American Heart Association. We turn now from London to San Francisco. The next speaker is Dr. William J. Kerr, President of the American Heart Association and newly elected President of the American College of Physicians. Dr. Kerr will explain the situation which confronts us from rheumatic heart disease in the United States.

Dr. William J. Kerr:

Lord Horder, we salute you from America. Our interests are happily joined upon this occasion. The American Heart Association is pleased to cooperate with the medical profession of Great Britain for this international broadcast so that the people in our respective countries may know the serious nature of one of our most crippling maladies—*rheumatic heart disease.*

Ladies and gentlemen of the radio audience, this disease is worthy of comment because it is related directly to the public health. It attacks children and young adults especially, and begins usually with symptoms and signs characteristic of rheumatic fever, generally known to the layman as inflammatory rheumatism. The damaging and more lasting effects are manifested in the heart. The blow comes when the individual is in the prime of life. The disability is usually progressive, and many of its victims die prematurely.

Let us consider the case of the child who suffers from rheumatic fever. After the stage of fever and painful joints and other less annoying complaints is passed, there is often a lull of months or years before there is a recurrence or the onset of complaints related to trouble in the heart. If the heart is seriously crippled, the capacity to do ordinary physical work is limited. The muscle fails and shortness of breath and swelling of the feet occur.

The loss of time and income in early and middle adult life because of this type of heart disease is greater than for any other chronic disease. According to the statistics of the United States Public Health Service, more than half of the deaths due to heart disease occur before individuals have lived out the normal span of life. Rheumatic heart disease alone causes at least 40,000 deaths every year, and the average age at which its victims die is 30 years.

Studies made in San Francisco have disclosed the fact that 20 per cent of workers on relief have shown some evidence of disease of the heart or circulatory system. Many of these workers had rheumatic heart disease. This is a greater incidence of such diseases than is to be found in the general population; presumably many of these workers, with their families, were on relief because of their physical incapacity. If these crippling diseases could be prevented, untold suffering would be avoided, and the benefits to individuals and their families and to the country would be enormous.

The American Heart Association has recognized the medical and economic importance of rheumatic heart disease. In many clinics and laboratories, studies are being undertaken to learn the facts about this disease, as you have heard from the other speakers. Already many promising beginnings have been made which we hope will be fruitful. It is now well recognized that the guilty offender, rheumatic fever, operates chiefly in temperate climates, generally during the late winter months, and chooses as victims chiefly children and adults who are poorly nourished. Even the well-to-do are not safe, but among them the incidence is very low. The disease occurs also, but less frequently, in our southern and southwestern states. Whether rheumatic fever is caused by some particular dietary deficiency, by an infectious agent, or by some combination of these with other factors is difficult at the moment to assert.

The American Heart Association is in a position to suggest how funds may be usefully employed to undertake studies which appear to offer some solution for our problems. In many centers laboratories are equipped to work independently or in cooperation with others on some phase of the problem. To date little support has been given to research projects in this field. The situation is not a hopeless one. New avenues of approach are being constantly opened, and methods of treatment have greatly improved the lot of the patient with heart disease. He can be taught to live within the capacity of his heart by curtailing his physical activity. The child with a damaged heart can be taught a sedentary occupation. When symptoms arise he can be given support by drugs and other means which will make his heart beat stronger. With the effective methods now known and in the hands of the intelligent physician, much good can be accomplished.

Dr. Howard W. Haggard, Commentator:

Dr. Kerr has defined the present status of one of our most serious maladies—rheumatic heart disease.

Control of this disease can come only from knowledge gained by medical research. At present such research is pitifully inadequately supported; it can become effective only when it receives the full aid of our public—a public informed and therefore aroused to pressing needs.

Dr. Homer F. Swift, of the Rockefeller Institute of New York City, will tell what is known of the cause of rheumatic heart disease.

Dr. Homer F. Swift (Certain Causative Factors in Rheumatic Heart Disease):

Rheumatic fever is apparently an infectious disease in which at least two causative elements must be considered: first, the hypothetical agent that induces the infection; and, second, the conditions which appear most favorable or unfavorable for the infectious agent to act.

Even though the nature of the causative agent is not definitely established, the conditions under which the disease appears and thrives can often be fairly well defined, and from this knowledge much can be done to impede its progress. We shall, therefore, consider mainly the so-called predisposing factors.

Rheumatic fever occurs chiefly in childhood, adolescence, and early maturity. In some instances the heart is unaffected, in others only temporarily involved, but in many it is permanently damaged, so that even if the infection be fully overcome, there are scars in the heart valves and muscle which interfere with the proper functioning of the organ. Cardiac involvement occurs most frequently in the rheumatic fever of childhood, and with each subsequent decade of life there is a steadily diminishing tendency for rheumatic fever to occur, and a diminishing liability for the heart to be attacked, even if a person contract the disease. This relationship between age and susceptibility or resistance is an important feature of the malady.

A second peculiarity is the tendency for the disease to recur in the same person. Apparently tissues, once involved, become favorable ground in which the infectious agent can work, and this is one of the serious aspects of rheumatism of the heart. One or two attacks may be well tolerated but, when they are numerous, more and more damage occurs until finally the heart is unable to respond to even slight extra bodily exertion.

While rheumatic heart disease occurs in people in all economic conditions, it is much more frequent among the poor, where crowding, undernutrition, and bad hygienic surroundings prevail. Moreover, there is often a tendency for several members of a family to have the disease.

Whether this is the result of the passage of a specific contagious element directly from one person to another, or is due to an hereditary vulnerability of certain people's tissues is, as yet, unsettled.

Climatic factors seem very important. Along the Atlantic seaboard and over continental North America, most cases occur in the spring. With the onset of warm weather rheumatic fever is more infrequent, and patients suffering from the disease tend to recover. In more southern climates the incidence is less, and the attacks are usually mild. Moreover rheumatic heart disease rarely occurs among inhabitants of the tropics, unless they have contracted it elsewhere.

More extensive studies of these climatic factors are needed, but the relatively lower incidence of rheumatic fever both during the northern summer and in the tropics is noteworthy; and this information may be used in attempting preventive treatment when it is economically possible to have a patient with rheumatic heart disease live in a favorable climatic environment for a long time. Unfortunately, because of financial difficulties, most sufferers from this disease are unable to make this move; and no sanatoria in especially favorable climatic situations, comparable to those that exist for tuberculosis patients, have been provided either by private endowments or public health authorities. By and large, there is a surprising lack of institutional facilities for the adequate care of rheumatic patients over long periods.

Certain infections are at times so closely connected with rheumatic fever and active rheumatic heart disease that their causative relationship must be seriously considered. These are streptococcal infections such as tonsillitis, sore throats, acute sinusitis, and middle ear disease, which are often forerunners of rheumatic fever as well as serious complications in a patient with active rheumatic disease. It is true that people suffer these respiratory diseases without developing rheumatic fever, but a person who has had rheumatic fever is in danger of a relapse or new attack if he contracts such a streptococcal infection. Even though this course of events does not definitely establish a causative relationship, the peculiar sequence suggests that these particular infections of the respiratory tract are very important in the life of a rheumatic subject.

While it has been possible to mention briefly only some of the indirect causative factors of rheumatic fever and rheumatic heart disease, attention to the various problems suggested will doubtless be important in the campaign which must be waged against this very crippling affliction.

Dr. Howard W. Haggard, Commentator:

Dr. Swift of the Rockefeller Institute has spoken on our present knowledge of rheumatic heart disease. Cure and prevention must await further medical research. But in the meantime there are thousands

already crippled by the disease; many thousands more may be injured before it is exterminated. With good medical care these cripples can be helped toward full and useful lives. Vital as is their need, there are in the United States few institutions devoted to the care of children with heart disease.

The next speaker in this international broadcast is Dr. T. Duckett Jones, of Boston, from the House of the Good Samaritan.

Dr. T. Duckett Jones (Treatment of Rheumatic Heart Disease in Children):

Since rheumatic heart disease is the result of rheumatic fever—itself a generalized disease with signs and symptoms often remote from the heart—both must be considered with regard to treatment.

At the beginning, the patient is usually quite ill and uncomfortable. Such patients are best treated in hospitals where good medical and nursing care are available. This is especially true of heart failure, which is not uncommon. As the acute phase of the disease subsides, the problem becomes one of prolonged bed care—rheumatic fever is a chronic disease persisting for months, and at times, several years. Especially during the first five or six years after the attack, the patient is prone to develop recurrences. These attacks are often preceded by sore throats or colds.

At the present time, this prolonged bed care may be satisfactorily obtained in only a few institutions. There is a great need for convalescent homes or hospitals where a long period of convalescence may be provided for cardiac patients. Despite the lack of statistics proving the value of such long bed rest, some of the obvious advantages may be mentioned:

(1) Following the acute illness, mild symptoms may continue for long periods.
(2) Even after the disappearance of the clinical, or obvious, symptoms, laboratory tests usually show a continuation of the activity of rheumatic fever.
(3) Rheumatic heart disease may develop or increase as long as active rheumatic fever continues.
(4) As long as there is even laboratory evidence of active rheumatic fever, recurring attacks are frequent.
(5) Continued rest in bed allows the body to conserve its entire energy for the fight against disease. It decreases the exposure to such infections as often cause an increase in rheumatic fever symptoms (most frequently colds and sore throats).
(6) Coincidentally with bed rest in the proper environment, the patient should be freed from varied anxieties, emotional or family difficulties.

(7) Such general recovery measures as proper food and ultraviolet light treatment are easily available.
(8) The education of the patient and family concerning the problem of rheumatic fever and rheumatic heart disease is an important consideration.
(9) A good psychological attitude on the part of the patient toward his disease can best be attained during such periods of long rest.
(10) The patient may be given bedside instruction, and his regular scholastic standing maintained.
(11) Vocational guidance and occupational handicrafts, important in such a disease, may be provided.

Following the cessation of active rheumatic fever, convalescent care may give abundant help during the period of gradual rehabilitation, prior to the return home and to a community life consistent with the existing degree of rheumatic heart disease. With the return to some semblance of normal life, frequent visits to the family or clinic physician are advisable. At this time the physician should be on the alert for evidence of renewed activity of rheumatic fever. He should advise the patient of the measures that may be helpful in keeping his general health and resistance at a high level. Some of the measures to be considered are rest periods, a well-balanced diet with suitable vitamins, the avoidance of fatigue and of sore throats and colds, the restriction of physical activity in some patients, and the betterment of home conditions.

The patient with moderate to severe rheumatic heart disease should be advised as to the degree of his physical activity. He should be educated to live within the limits of his heart reserve and trained for sedentary occupations when necessary. The use of drugs at times helps considerably to increase the efficiency of the heart.

There are no sure, rapid cures for rheumatic fever or rheumatic heart disease. Long care is essential. In some instances, the removal of tonsils, abscessed teeth, and other sources of infection is helpful, but will not cure the disease. Such procedures at the wrong time may even result in recurrences.

There are encouraging features. Of one thousand young patients given prolonged care and careful observation, 75 per cent are alive. The majority of them lead active, physical lives ten years after the onset of their disease. Six hundred of the thousand have no necessary restrictions of their activity, although nearly half of these have a slight degree of rheumatic heart disease. In only 150 are there moderate to severe restrictions of their lives due to rheumatic heart disease.

Further studies and varied laboratory investigations are needed. The combined interest of the medical profession and the public should result in the solution of many of the problems of rheumatic fever and rheumatic heart disease.

Dr. Howard W. Haggard, Commentator:

Ladies and gentlemen, you have heard the four speakers on the first international health broadcast: Lord Horder, of London; Dr. Kerr, of San Francisco; Dr. Swift, of New York; and Dr. Jones, of Boston. They have defined for you one of the major medical problems of today—the problem of rheumatic heart disease. In enlisting your aid these physicians have presented only bare facts. But behind those facts, treated with such restraint, lie the thousands and hundreds of thousands of heart-breaking scenes—the parents, the homes, the stricken children—each is a tragedy of life lost or life blighted by a disease which we must eradicate.

There must be medical research; there must be adequate care. There will be when you are determined that there shall be. It is public opinion shaped by sound information—information such as you have heard this evening—which determines what will be done.

For those who wish more information on rheumatic heart disease a special pamphlet has been prepared by the American Heart Association, New York City. It will be sent upon receipt of 5 cents in postage.

And now, ladies and gentlemen, we bring to a close the first international health broadcast—a pioneer venture.

Closing Announcement:

This evening the National Broadcasting Company has brought you The First International Health Broadcast, conceived by Irvington House, a Sanatorium for Children with Rheumatic Heart Disease, and sponsored by the American Heart Association. The speakers heard during this program, defining the major medical problem of rheumatic heart disease, were Lord Horder, of London; Dr. Kerr, of San Francisco; Dr. Swift, of New York; and Dr. Jones, of Boston. They were introduced by Dr. Howard W. Haggard, Professor of Applied Physiology at Yale University.

For those who wish more information on rheumatic heart disease a special pamphlet has been prepared by the American Heart Association and will be sent upon receipt of 5 cents in postage. Address your request to the American Heart Association, 50 West 50th Street, New York.

Department of Clinical Reports

ADAMS-STOKES SYNDROME INDUCED BY TRANSIENT, RECURRENT VENTRICULAR FIBRILLATION*

CASE REPORT

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THERE are comparatively few cases of ventricular fibrillation in man recorded in the literature. I have been able to find reports of only 24 individual cases, together with 22 additional cases recorded by Turner,[1] Hanson,[2] Kahn and Goldstein,[3] Robinson,[4] Dieuaide and Davidson,[5] and Sigler, Stein and Nash[6] in which electrocardiographic studies of the dying human heart revealed ventricular fibrillation as a transient phenomenon. In some of the reported cases the electrocardiographic evidence is not convincing.

One reason for the scarcity of reports is that ventricular fibrillation is usually fatal. The longest attack with recovery was six minutes in a case reported by Schwartz and Jezer.[7] Another reason is that the disorder cannot be recognized clinically, and, unless electrocardiographic studies are made at death or in all cases of the Adams-Stokes syndrome, it may be missed.

The following case is reported because of the scarcity of such reports and because it offers additional information on the nature of the disorder.

CASE REPORT

L. F., a man 58 years of age, consulted me March 7, 1936, because of weakness, dyspnea, and retrosternal pain occurring on exertion. The symptoms followed an attack of "the grippe" three weeks previously. His family and past histories were essentially negative. He had been married thirty years and had never had any children. He had had no serious illness or venereal disease. His habits were good, but he always worried about the most trivial matters.

The physical examination showed a somewhat undernourished man whose height was 68 inches and weight 142 pounds. He had no pallor or cyanosis. There was slight enophthalmos; the pupillary reactions were normal to light and in accommodation. The gums were the seat of pyorrhea, and the pharynx was chronically inflamed. There was moderate peripheral arteriosclerosis and the blood pressure was 150/70. The dorsal spine was moderately kyphotic and the chest somewhat barrel-shaped, with considerable depression at the lower end of the sternum.

The heart was slightly enlarged to the left, and the aortic arch was widened and tortuous. The heart rate varied between 33 and 70 per minute; the beating was regular except for frequent ventricular extrasystoles. The first and second sounds

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were accentuated at the apex but diminished at the base. There was a short, rough systolic murmur which was loudest at the apex and was transmitted to the anterior axillary line, to the left sternal border, and across the base.

Examination of the lungs showed some prolongation of expiration over both upper lobes anteriorly, and an occasional moist râle at the bases posteriorly. The abdomen was negative except for a bilateral inguinal hernia. The patient was moderately sensitive to pain, and stimulation of his carotid sinus elicited a moderate cardio-inhibitory response.

The clinical diagnosis was general arteriosclerosis, coronary sclerosis, atherosclerosis with some calcific infiltration of the aorta; slight left ventricular enlargement; myocardial fibrosis; partial auriculoventricular block and the anginal syndrome; emphysema; and bilateral inguinal hernia.

I saw the patient on many occasions thereafter; he seemed to improve symptomatically when his activities were restricted. Objectively, however, there was a gradual diminution in the intensity of the first sound, which seemed to split into two sounds when the heart rate slowed. His systolic blood pressure varied between 120 and 150, and his diastolic between 70 and 90.

On Nov. 11, 1936, he was found in the bathroom unconscious and in convulsions. These attacks recurred subsequently with great frequency and severity, sometimes as often as twenty times a day. A severe attack was characterized by a gradual onset of unconsciousness, marked pallor, suspension of respiration, disappearance of the pulse and heart sounds, and the assumption of a motionless state, which was soon followed by cyanosis and convulsions of variable duration and intensity. When the convulsion subsided, the face would become flushed, and there would be a gradual return to consciousness. Confusion of thought and disorientation usually followed such attacks. Mild attacks were characterized merely by confusion, dizziness, and more or less stupor or dulled sensitivity. Both adrenalin and quinidine aggravated the symptoms, and no other drug was of any avail. *Intravenous injection* of 50 c.c. of 50 per cent glucose solution was tried and gave considerable relief. The fatal attack occurred Dec. 30, 1936.

Electrocardiographic Observations.—Several electrocardiograms were made before the onset of the Adams-Stokes syndrome, and long tracings were obtained before, during, and after a prolonged seizure. Fig. 1*A* is a tracing obtained March 7, 1936. It shows partial 3:2 auriculoventricular block. The auricular rate is about 100 per minute and the ventricular rate 66. The auricular impulses are of normal sinus origin. The P-R interval of the effective impulses is 0.18 sec. The intraventricular conduction time is 0.12 sec. The QRS complexes are slurred and notched, and there is left axis deviation. The T-waves are markedly positive in Leads I and II and negative in Lead III. The curve shown in Fig. 1*B* was obtained May 26, 1936. It shows partial 2:1 auriculoventricular block, and occasionally a 3:2 relationship. The auricular rate is 62 to 66 and the ventricular rate, 31 to 44. The effective A-V conduction time, as well as the character of the ventricular complexes, is the same as on the previous occasion. The voltage, especially that of the T-wave, however, is definitely lower. In Lead III the T-wave is now diphasic.

Tracings were obtained at various times between paroxysms, and during short periods of drowsiness and transient loss of consciousness, pro-

longed unconsciousness and convulsions, immediately following the convulsions, and after the return to consciousness. Fig. 2 (*A* to *U*) shows selected portions of the electrocardiograms depicting the various phases.

Before a major paroxysm the auricular rate was 115 to 120 per minute, and the ventricular complexes appeared irregularly. Some of the ventricular complexes were of the supraventricular type with prolongation of intraventricular conduction time to 0.12 sec., as in Fig. 2, *A* and *C*. These are frequently interrupted or completely replaced by showers of ectopic ventricular impulses originating in various parts of the ventricles, as in Fig. 2, *A*, *C*, *D*, *F*, and *I*. These impulses frequently form short paroxysms of tachycardia, usually at a rate of about 220 per minute, as in Fig. 2, *B* and *E*. In nearly all of these short paroxysms some of the features of the QRS complexes are decipherable. The contiguous impulses in each group bore a close resemblance to each other but usually differed from those of another group. Occasionally a sudden change was noted in the appearance of the complexes in the same group. In

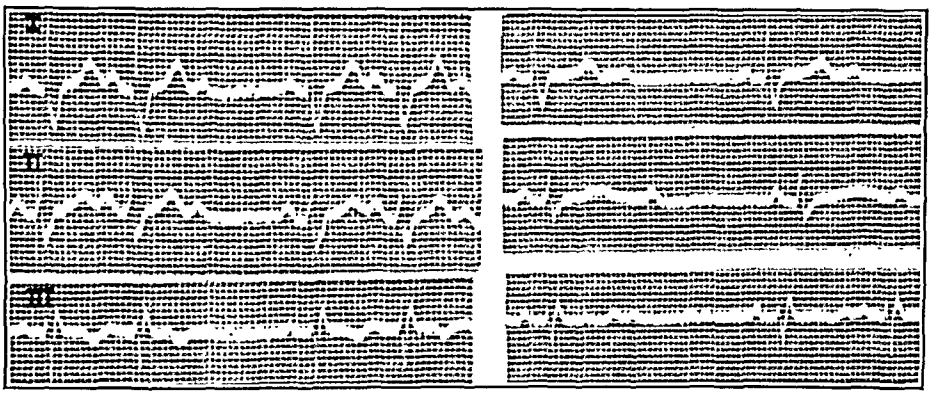

Fig. 1.—*A*, Three standard leads, March 7, 1936. Partial 3:2 auriculoventricular block, auricular rate 100, ventricular rate 66: effective auriculoventricular conduction time 0.18 sec.; intraventricular conduction time 0.12 sec.; slurred and notched QRS complexes.

B, Three standard leads, May 26, 1936. Partial 2:1 and occasional 3:2 auriculoventricular block; auricular rate 62 to 66, ventricular rate 31 to 44; voltage of all complexes lower.

such instances two or three complexes of similar appearance were succeeded by a complex of intermediary appearance, as seen in Fig. 2, *E*. The auricular rate was always slightly accelerated during and after such short paroxysms, but after a long paroxysm it was always slowed. After some paroxysms the auricular waves were inverted, as in Fig. 2, *I*.

The appearance of the ventricular complexes in any paroxysm depended upon the rate. Above 250 per minute the complexes assumed the appearance of undulations of various heights and shapes, and the QRS and T components were not decipherable, as in Fig. 2, *G*, *J*, *K*, *L*, *M*, *N*, and *O*. As slowing occurred, the QRS and T components became more or less evident again, as in Fig. 2, *H*, *P*, and *Q*.

Regardless of the appearances of the oscillations in each paroxysm, the duration of each cycle is almost an exact submultiple of the rate. Thus,

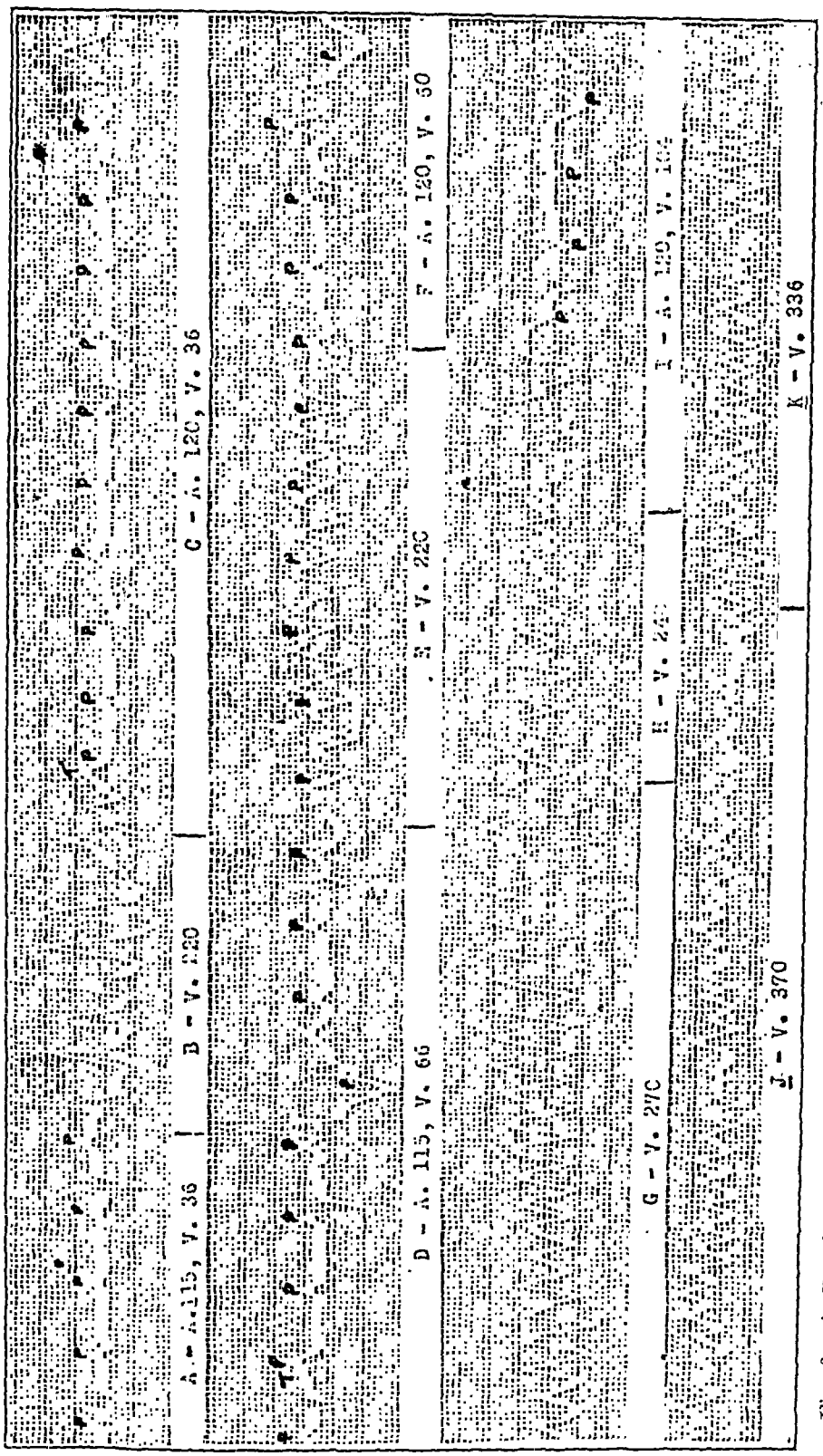

Fig. 2.—*A*, Regularly recurring auricular impulses; two supraventricular impulses with different spread. *B*, Ventricular tachycardia, deformity of ventricular impulses; *C*, auricular and ventricular impulses, supraventricular type, ending by ventricular premature contraction; *D*, multifocal ventricular premature contractions; *E*, short paroxysm of ventricular tachycardia, marked deformity of impulses; *F*, acceleration of auricular rate following paroxysm; *G*, recurring ventricular oscillations, more rapid rate with disappearance of the QRS markings; *H*, slowing of rate and reappearance of markings; *I*, inverted auricular impulses following paroxysm; *J*, rapid ventricular oscillations; *K*, somewhat slower ventricular oscillations. *A*, auricular rate; *V*, ventricular rate.

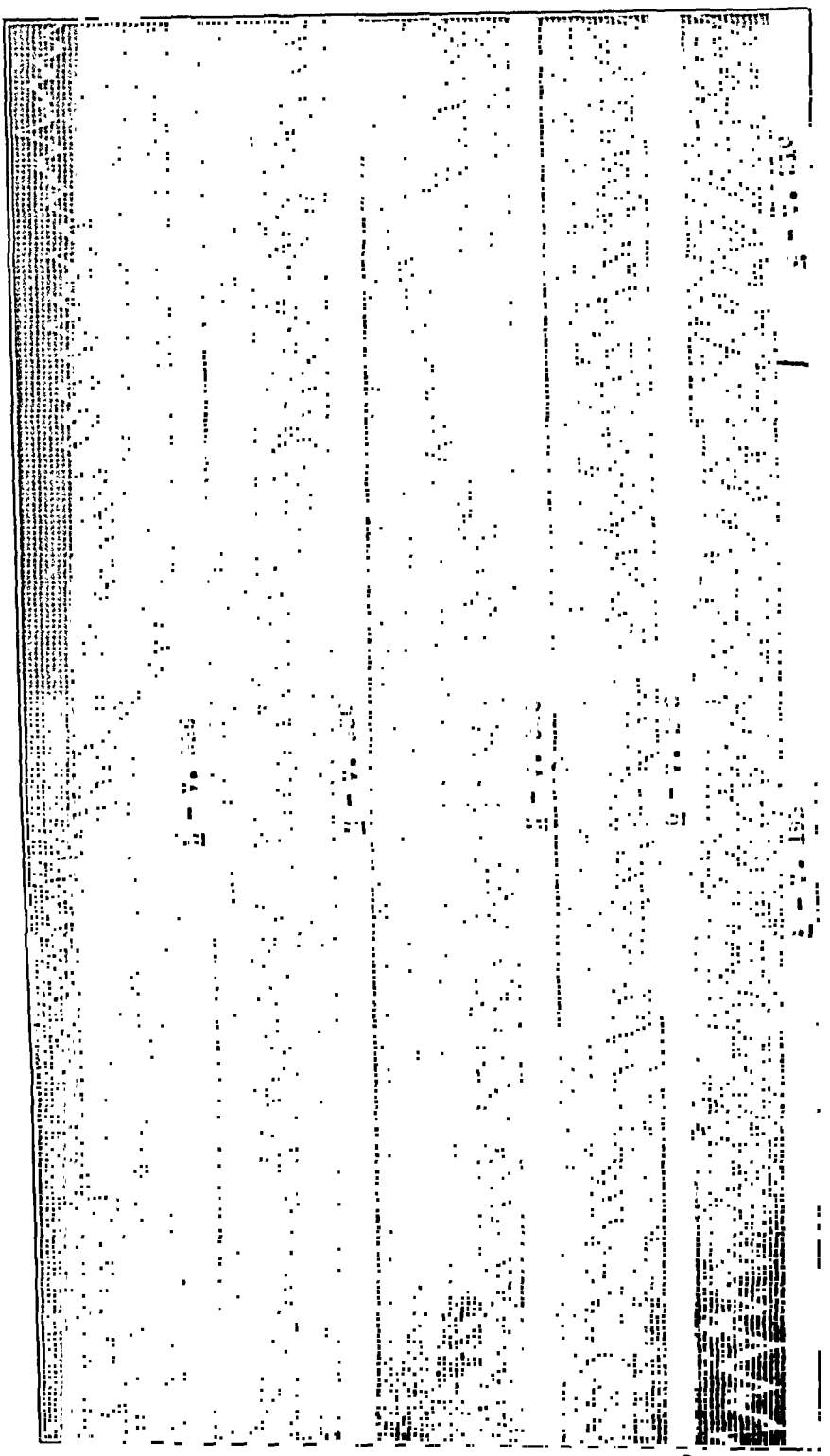

Fig. 2 Cont'd.—*L*, *M*, *N*, and *O*, Continuous oscillations with progressively slowed rate, marked deformity of the oscillations, no *isoelectric level*; *P and Q, continuation of O with marked* slowing of rate and reappearance of recognizable ventricular complexes, although markedly deformed at first. Isoelectric level present and complexes are of almost equal voltage.

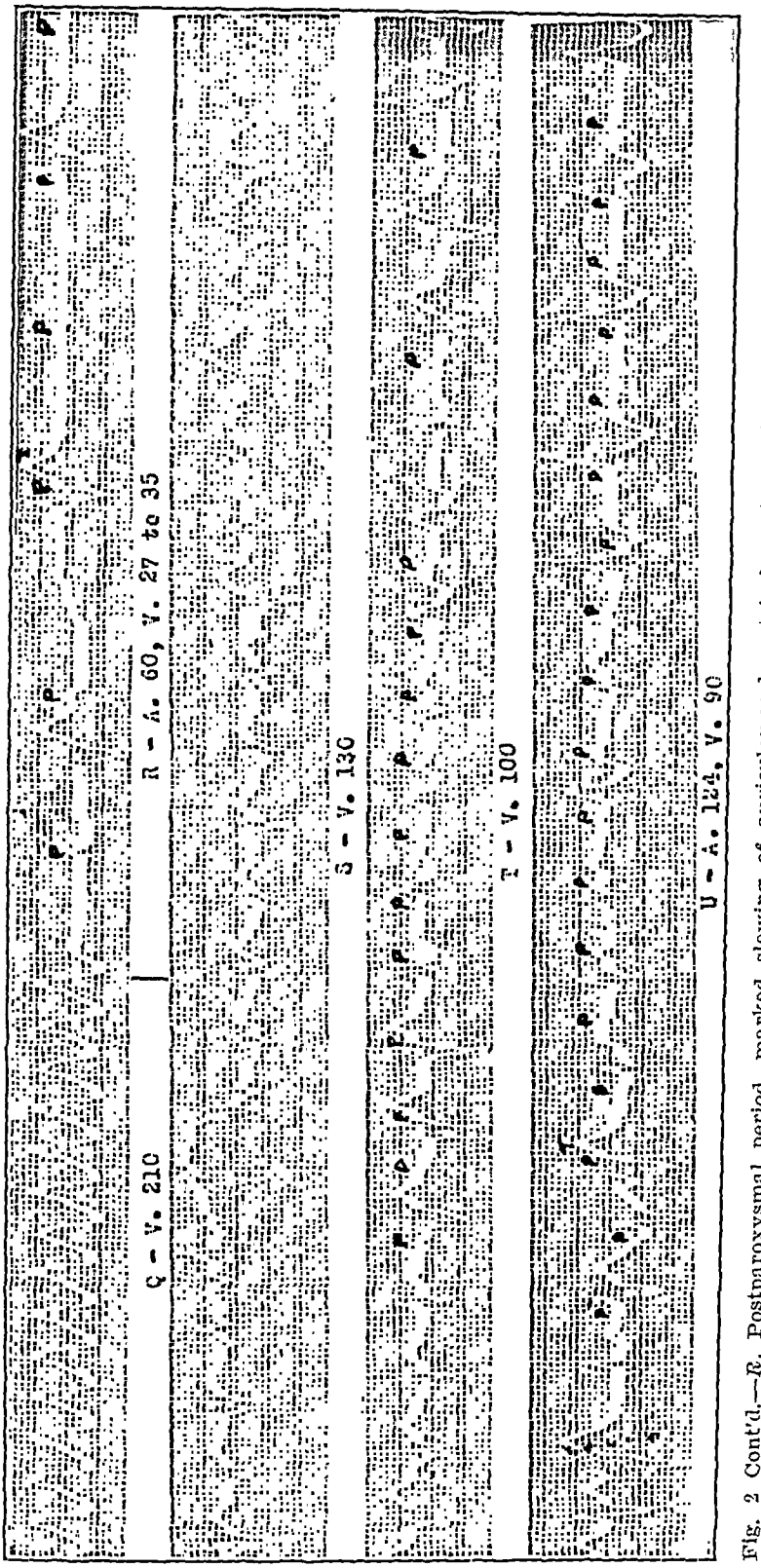

Fig. 2 Cont'd.—*R*, Postparoxysmal period, marked slowing of auricular and ventricular rate. *S*, *T*, and *U*, Multifocal idioventricular impulses with progressive slowing of rate. *A*, auricular rate; *V*, ventricular rate.

in Fig. 2, *G*, when the rate is 270 per minute, the duration of each complete cycle is approximately 0.20 sec., whereas in Fig. 2, *J*, when the rate is 370 per minute, the average cycle measures about 0.16 sec.

The highest rate of oscillations in the entire series was about 370 per minute, shown in Fig. 2, *J*. In all long paroxysms the initial rate was always high, and, as the condition progressed, it gradually slowed, as in Fig. 2, *J*, *K*, *L*, *M*, *N*, and *O*, which comprises nearly an entire paroxysm. As the rate comes down to 195 per minute, as in Fig. 2, *P*, the QRS complexes are again clearly decipherable. The oscillations become more regular, and the voltage more uniform. This equality is more marked near the termination of the paroxysm, seen in Fig. 2, *Q*, even though the rate again increases slightly.

Superimposed on the main oscillations are numerous fine undulatory movements, caused undoubtedly by somatic muscular tremors.

The termination of a long paroxysm was always abrupt, as shown in Fig. 2, *R*. The auricular impulses reappear at a rate of 60 per minute, with moderate sinus arrhythmia. The ventricular impulses are of a supraventricular type with prolongation of the intraventricular conduction time to 0.12 sec. and with marked slurring and notching. The rate is 27 to 35 per minute, and the beating is somewhat irregular. This period lasted about five minutes and was followed by ectopic ventricular impulses originating in various foci (Fig. 2, *S*, *T*, and *U*) which entirely replace the usual impulses. The auricular rate is accelerated to 124 per minute and the ventricular rate to 130 in Fig. 2, *S*, coming down to 100 in *T* and to 90 in *V*. The auricular impulses are frequently buried.

SUMMARY

A case of recurring Adams-Stokes syndrome induced by transient ventricular fibrillation is reported. The attacks occurred at intervals of about seven weeks and recurred as often as twenty times a day. The longest individual attack lasted three and one-half minutes.

The prefibrillation phase was characterized by complete auriculoventricular dissociation with recurring multifocal ventricular impulses. The period of actual fibrillation presented a phase resembling paroxysmal tachycardia and a later, more advanced phase of irregular rapid undulatory movements. The highest oscillatory rate was 370 per minute; the rate was highest at the beginning of the paroxysm, and slowed gradually as it progressed. When the rate slowed to about 200 per minute, the electrocardiogram again assumed the appearance of ventricular paroxysmal tachycardia. The time interval of a complete oscillatory cycle was almost an exact submultiple of the rate of the group of oscillations in which that cycle belonged.

The immediate postfibrillation phase was characterized by abrupt cessation of fibrillation and very slow resumption of auricular and ventricular activity.

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PRIMARY TUMOR OF THE HEART PRODUCING AN UNUSUAL CARDIAC SHADOW IN THE ROENTGENOGRAM*†

Report of a Case

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CASES of tumor of the heart are reported from time to time, and in a few instances the diagnosis has been made before death.[1-6] The presence of a tumor may be suspected when roentgenograms show that there is localized enlargement of the heart or irregularity in its contour.[7] In the following case, although the diagnosis was not made, a tumor within the left auricle was found to be responsible for roentgenographic changes of this kind.

History.—The patient was a married Guatemalan woman, 37 years of age. On admission to the hospital she complained of cough, pain in the chest and lower abdomen, pains and aches in the extremities, and diarrhea. These symptoms had been present for only a few days. Little other information could be obtained regarding her present illness.

In childhood she had had malaria and smallpox. Her tonsils had been removed when she was 22 years old. Six years before admission, she had contracted gonorrhea, and pelvic inflammation had resulted; she married shortly afterward but never became pregnant. One year before admission salpingo-oöphorectomy and appendectomy were performed, and during her convalescence she developed what was diagnosed as bronchopneumonia. Six months later she began to complain for the first time of attacks of wheezing and difficulty in breathing. These symptoms were associated with weakness and dyspnea on moderate exertion. The attacks were thought to be asthmatic and were relieved to some extent by epinephrine.

Physical Examination.—The patient was a moderately obese, dark-complexioned woman who was orthopneic and perspiring profusely. She appeared to be weak, complained of a feeling of retrosternal "tightness," and had an expiratory wheeze. The integument, lymph nodes, head, and neck were normal. The chest was symmetrical in outline. The breasts were small. Respiratory movements were somewhat limited but were equal on both sides. Except for prolongation of the expiratory phase, auscultation of the lungs showed nothing abnormal. The area of cardiac dullness extended 11 cm. to the left of the midsternal line in the fifth intercostal space. All of the heart sounds were accentuated, especially the pulmonic second. The rate was 120, the beating regular. No adventitious sounds were audible. The peripheral vessels were normal. The blood pressure was 110/80. The abdomen showed an old lower midrectus scar and was moderately tender to palpation over both lower quadrants. There were no abnormal findings in the extremities or back and neurologic examination was negative. Vaginal examination revealed a tense, firm, very tender mass, with much surrounding induration, in the right fornix. Less induration was noted on the left side. Rectal palpation confirmed these findings.

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†Received for publication Feb. 18, 1938.

Laboratory Examination.—A catheterized specimen of urine was normal except for the presence of a faint trace of albumin and a few granular casts. The blood Wassermann reaction was weakly positive (+), and the Kahn test strongly positive (++++). The hemoglobin was 12.4 gm. per 100 c.c. and the erythrocyte count 4,100,000 per cubic millimeter; the leucocyte count varied from 17,600 to 24,000 per cubic millimeter, and the differential leucocyte count showed that 91 to 93 per cent of the cells were polymorphonuclear leucocytes. The sedimentation time of the erythrocytes (Linzenmeier's method) was 18 mm. in 17 minutes. Blood cultures were negative on two occasions. The stool showed no abnormalities.

Subsequent Course.—During her stay in the hospital, the patient's temperature averaged 103° F., without much fluctuation. The pulse rate varied between 100 and 130 beats per minute, and the respirations between 20 and 36 per minute.

It was thought that the patient had a pelvic abscess and possibly an atypical pneumonia. Because of the latter possibility, a roentgenogram of the chest was taken, which was interpreted by Dr. A. J. Williams as follows: "The heart shadow

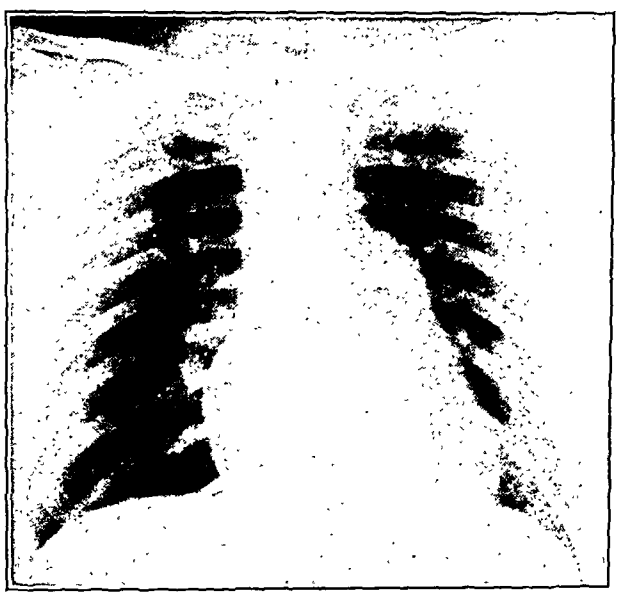

Fig. 1.—Posteroanterior roentgenogram, showing bulge in the upper left portion of the cardiac shadow due to tumor within the left auricle.

is enlarged both to the right and left. There is a large bulge in the region of the pulmonary conus. The aortic arch is not visible; it is either unusually small or has been displaced to the mid-line by the enlarged pulmonary conus. The lung fields are essentially clear. Mitral heart disease can be excluded by the absence of enlargement of the upper right border and of pulmonary vessel engorgement. The heart outline is that commonly produced by congenital anomalies such as an interatrial septal defect or a patent ductus arteriosus." (Fig. 1.)

The patient was prepared for drainage of the pelvic abscess. A few minutes after the induction of nitrous oxide and oxygen anesthesia, the heartbeat and respiration stopped. Administration of the anesthetic was discontinued, and stimulants were given, including epinephrine intracardially. The heartbeat and respiration were restored, and the blood pressure rose to 110/80, but the patient remained unconscious. Without further anesthesia, the abscess was opened by a posterior colpotomy, and drained of 200 to 300 c.c. of foul-smelling, purulent material which on culture yielded a variety of aerobic and anaerobic cocci and bacilli, but no *B. coli.*

The patient continued in a comatose state, and, except for spasmodic contractions of the muscles of the face and upper extremities, did not respond to further stimulation. She expired nine hours after being returned to the ward.

*Post-Mortem Examination.** (excerpts).—"Each pleural cavity contained about 200 c.c. of slightly cloudy, bloodstained, amber fluid. There were a few adhesions but the pleural surfaces were thin and glistening. The lungs were soft, somewhat soggy, and crepitation was diminished. The cut surface was rather moist, slightly

Fig. 2.

Fig. 3.

Fig. 2.—Tumor in the left auricle, intact.
Fig. 3.—Tumor in the left auricle, after incision.

brownish, and displayed the usual pulmonary structure. The bronchioles were not thickened, and the bronchi contained small amounts of frothy fluid. Each lung weighed 345 gm.

"The pericardial sac had a clean, glistening lining and held a few cubic centimeters of bloodstained fluid. On the anterior surface of the heart there was a small mark left by the insertion of a needle for the administration of adrenalin. The heart itself was red-brown, moderately firm, and rather small in

*Made by Dr. J. Carr and Dr. N. Rudo.

size. The epicardium contained a small amount of fat. The heart was opened in the usual manner, and the valves and chambers were examined. The wall of the right ventricle was slightly thickened, measuring about 0.5 cm. The tricuspid valve measured 10 cm. in diameter, and the pulmonary valve, 5 cm. In the left auricle

Fig. 4.

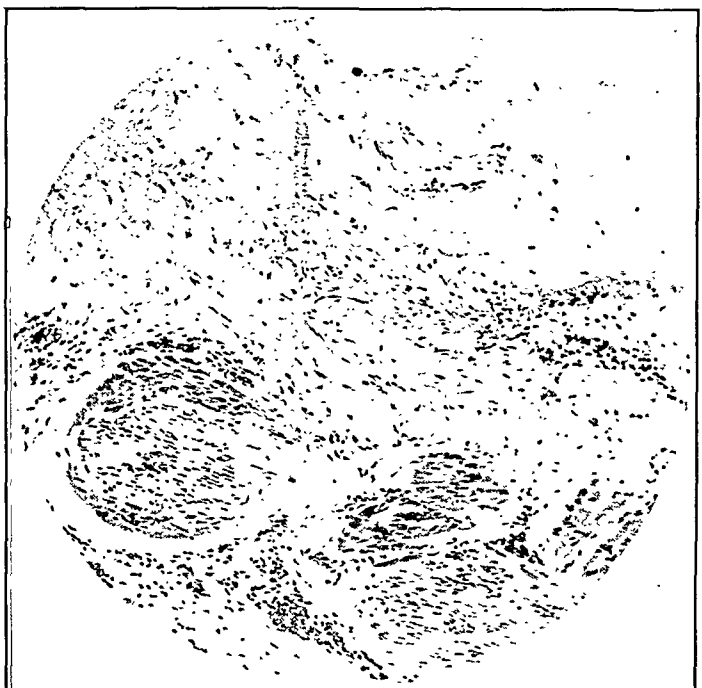

Fig. 5.

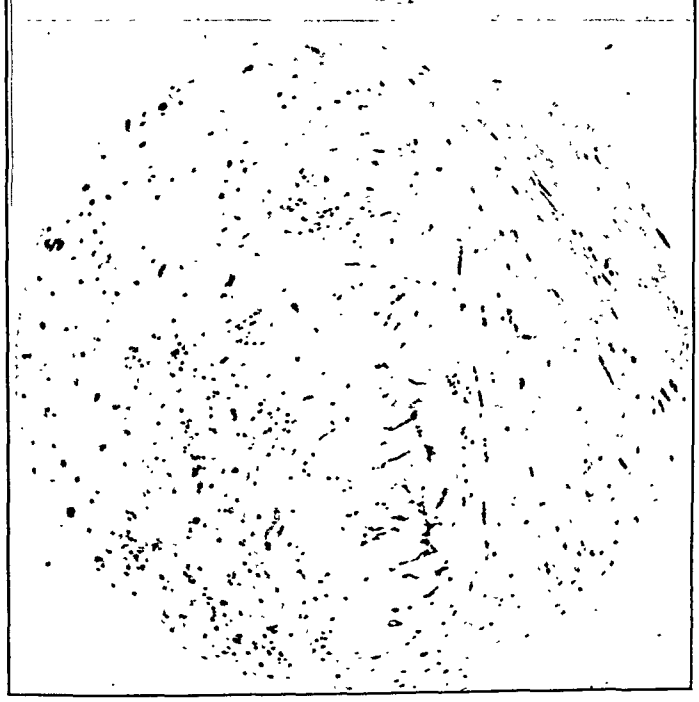

Fig. 4.—Photomicrograph of the base of the tumor, showing fragmented cardiac muscle tissue and tumor cells (×160).

Fig. 5.—Photomicrograph of the tumor (×100).

there was a large, irregularly rounded, glistening mass attached to the interauricular septum at the site of the fossa ovalis. The bulging of this mass through the fossa could be seen in the right auricle. The mass measured between 3.5 and 4 cm. in

diameter. Its color varied from yellow to red, and it had a slightly transparent appearance. It was somewhat rubbery in consistency and did not appear to be organized to any great extent. On the surface there were a few minute, rough gray flecks. As stated above, this ball-like mass was attached only to the medial wall of the left auricle; it filled the auricle almost completely. The lower part of the mass extended into the mitral orifice but did not seem to project far enough to interfere with the action of the valve. The mitral valve measured 8 cm. in diameter, and the aortic valve, 5 cm. The wall of the left ventricle was 1 cm. thick. No thrombus or abnormality was found elsewhere; the coronary orifices and vessels were open. The musculature showed grossly no evidence of fibrosis or infarction. The heart weighed 200 gm. (Figs. 2 and 3.)

"*Microscopic Examination.*—The auricular mass was composed of a relatively acellular, myxomatous, finely fibrillar material in which were thin-walled blood vessels and spindle-shaped connective tissue cells. The free surface was covered by a single layer of endothelium that was reflected from the wall of the auricle. At the base of the tumor there was a small amount of degenerate heart muscle with sparse lymphocytic infiltration (Figs. 4 and 5). There was no invasion of the interauricular septum, although it was somewhat compressed and the muscle was atrophic. The remainder of the heart muscle was not remarkable.

"Although a complete autopsy study was made, the only other important abnormality was generalized peritonitis; the abdominal cavity contained 1,000 c.c. of purulent fluid. An extensive pelvic abscess was present, but the pelvic structures were so distorted that it was impossible to determine its exact origin."

DISCUSSION AND CONCLUSIONS

It is seldom that a primary tumor of the heart is diagnosed during the life of the patient. The clinical manifestations depend upon the size and location of the tumor. A lack of any other adequate explanation for abnormalities in the size and shape of the heart or in the mechanism of the heartbeat, and for abnormal auscultatory signs, should suggest the possibility of a tumor of the heart.

In our case, the difficulty in interpreting the patient's rather indefinite history of respiratory and possible circulatory embarrassment was due partly to the presence, in addition, of a severe pelvic and abdominal infection that drew attention from the intrinsic cardiac disturbance. No adequate clinical study of her circulatory system was made. However, the unusual outline of the cardiac shadow seen in the roentgenogram of the chest indicated the presence of an abnormality of the circulatory system. This shadow was thought to be due to an abnormality of the pulmonary conus or artery, although no clinical signs of disease of these structures were present. The roentgenogram of her chest was obtained in order to investigate the possibility of pulmonary infection, rather than because of any positive evidence of circulatory disease as indicated by the physical examination.

It is believed that this patient died because of the presence of overwhelming infection but that the tumor in the left auricle, by interfering with the normal function of this chamber, was definitely a contributing factor.

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Department of Reviews and Abstracts

Selected Abstracts

Graybiel, Ashton and White, Paul D.: Diseases of the Heart: A Review of Significant Contributions Made During 1937. Arch. Int. Med. 61: 808, 1938.

This annual review includes all the literature of the past year with editorial evaluations. It is in the usual form. Notice has been given that if there is sufficient demand, reprints of each year's reviews will be prepared for distribution.

McCULLOCH.

Wolf, J., Mohr, M., and Kröger, E.: The Blood Supply of the Kidney After Ligation of Its Main Artery Supply. Ztschr. f. d. ges. exper. Med. 100: 485, 1937.

Ligation of the renal artery of one kidney causes hypertension and an increase in blood tyramine. It was found that the outflow of the renal vein from such a kidney is still one-tenth to one-fourth that from the other kidney. The blood comes in from the collaterals through the kidney capsule.

KATZ.

Stoll, A.: New Developments in the Chemistry of Cardiac Glucosides. Ztschr. f. Kreislaufforsch. 30: 221, 1938.

The close relation of glucosides to bile acids and sterols has recently been shown and the structural formulas for the various genins like strophanthidin, digitoxigenin, gitoxigenin, dixogenin, and scillaridin A have been established. New glucosides have been found in certain plants and from these previously known glucosides have been split off as a result of enzymatic action. Work of this sort which the author details has permitted the isolation of pure glucosides and thereby allowed better standardization of these digitalis derivatives for clinical use.

KATZ.

Schneider, D.: Clinical Observations of the Action of Veritol. Klin. Wchnschr. 16: 736, 1937.

The preparation, veritol, is an oxyphenylmethylaminopropan. In 120 patients with collapse it caused a definite rise in blood pressure of longer duration than other drugs tried. Its action on intramuscular and intravenous use is rapid in onset. It has no effect on respiration and only a slight accelerating effect on the pulse. The blood sugar level is unaffected. Its action, as Rein has shown, is to empty the blood content of the blood reservoirs, to increase the venous tone, and to increase the minute volume blood flow.

KATZ.

Tislowitz, R., and Pines, I.: The Vagotonic Action of Vitamine B_1 on the Normal Dog's Heart. Klin. Wchnschr. 16: 923, 1937.

One to 2 mg. of pure vitamin B_1 daily causes sinus bradycardia and arrhythmia. This also occurs in acute experiments, one to two hours after 10-20 mg. of the vitamin. The possibility of using this vitamin in paroxysmal tachycardia is suggested.

KATZ.

Brandenburger, P.: Another Cause for Adams-Stokes Attacks. Ztschr. f. Kreislaufforsch. 30: 246, 1938.

Three cases are presented in detail in which cardiac standstill with dizziness and fainting followed sudden changes in the position of the head. In these patients an enlarged parotid gland was found which pressed on the carotid sinus, and the phenomena are attributed to this stimulation of the carotid sinus.

KATZ.

Sturm, A., and Dauter, H.: The Depressor Action of Choline Derivatives and Histamine (Observed in Man). Arch. f. exper. Path. u. Pharmakol. 185: 368, 1937.

Acetylcholine can cause blood pressure falls lasting for as long as two hours due apparently to cardiac action only. Doryl has a similar effect on blood pressure apparently due to vascular action. Histamine causes capillary enlargement and arterial and arteriolar dilatation, but this by causing increased venous return may lead to an initial blood pressure rise before the blood pressure fall appears.

KATZ.

Hoen, E., and Neuthard, A.: Pharmacologic Studies on the Minute Volume Output of the Normal Human Heart. Arch. f. exper. Path. u. Pharmakol. 185: 293, 1937.

Grollman's acetylene method for measurements was used. Caffeine, theobromine, and theophylline all increase minute cardiac output in ten to fifteen minutes, the increase being about 200 per cent for caffeine, 150 per cent for theophylline, and 100 per cent for theobromine. The action of caffeine lasts longest. The action of theobromine is irregular. Cardiazol (metrazol) increased minute volume output only 50 per cent; coramine, 125 per cent.

KATZ.

Schöne, G.: The Magnitude of the Circulation in Paroxysmal Tachycardia. Klin. Wchnschr. 16: 804, 1937.

The method of Broemser and Ranke for determining minute volume of the circulation was used on two patients. In one with 1:1 auricular flutter (rate 297) the minute volume output during the attack was 1.89 liters, compared with a rate of 4.02 liters when the heart rate was normal. In the second case with a nodal tachycardia and rate of 154, the minute volume output decreased from 3.16 liters before the attack to 2.74 liters during the attack. In the first patient there was x-ray evidence of cardiac enlargement attributed to the excessive tachycardia.

KATZ.

Von Pein, H.: The Measurement of Gaseous Metabolism as a Test of Heart Function. Ztschr. f. klin. Med. 132: 227, 1937.

Oxygen consumption during stair climbing was measured, the expired air being collected in a Douglass bag. The oxygen debt and exercise excess oxygen consumption were increased in heart failure. In normal subjects the excess oxygen consumption is dependent on the amount of work, and the oxygen debt, on the rate of work. This test, the author found, permitted the early recognition of heart failure.

KATZ.

Von Gruber, Z.: The Electrocardiogram With Short P-R and Broadened QRS Complex. Ztschr. f. Kreislaufforsch. 30: 100, 1938.

This is a report of six cases. The author offers as an explanation the idea that under the influence of the sinus impulse, an extrasystole in the right auricle near the A-V junction is set up, with fixed coupling. The P-wave of this extrasystolic beat fuses with the QRS complex resulting from the spread of the sinus impulse to the ventricle and makes it appear long and the P-R short.

KATZ.

Huttmann, A.: The Auricular Electrocardiogram in Cor Bovinum. Ztschr. f. Kreislaufforsch. 30: 171, 1938.

Eight cases of cor bovinum are reported in which the P-wave was abnormally tall, broad and notched, and sometimes inverted in Leads II and III and sometimes splintered in Lead I. This is attributed to auricular hypertrophy.

KATZ.

Fröhlich, R.: The Electrical Axis of the Heart. Ztschr. f. Kreislaufforsch. 30: 251, 1938.

This is a mathematical and theoretical discussion to show that the "electrical axis" and the magnitude of the "manifest potential" are not in general related to the magnitude of the potentials developed in the heart. They are of value, however, in measuring the peripheral electrical field.

KATZ.

Kienle, F.: Chest Leads With Different and Indifferent Electrodes. Arch. f. Kreislaufforsch. 2: 224, 1938.

This is a 42-page presentation dealing with chest leads. The author used as his indifferent electrode a lead from copper wire mesh of a large electrode upon which the patient was placed. This electrode was grounded. Characteristic changes over the left ventricle were found in diseases of this chamber, and over the right ventricle when this was diseased. These consisted of inversion of T and depression of S-T (new technique).

KATZ.

Braun Menendez, E., and Moia, B.: Rapid Nodal Rhythm Alternating With Sinus Rhythm in Congestive Heart Failure. Rev. argent. de cardiol. 4: 329, 1937.

Rapid nodal rhythm alternating with sinus rhythm and auricular extrasystoles appearing in the same record taken in a man aged 45 years with congestive heart failure is described.

The strong jugular pulsations and ingurgitation, together with a palpable hepatic pulse, suggested a tricuspidal insufficiency. The graphic records showed, however, that the jugular wave and hepatic pulse were really due to the auricular contraction, unable to discharge its contents in the ventricle because of the simultaneous contractions. The phonocardiogram also showed a marked intensification of the first heart sound due to a true summation of auricular and ventricular sounds.

During the sinus rhythm both the venous pulse and heart sound records appeared normal again, and the hepatic pulse almost entirely vanished.

An esophageal lead allowed a correct visualization of the retrograde auricular wave in the electrocardiogram.

Upon moderate digitalization the nodal rhythm disappeared.

AUTHOR.

Chen-Lang Tung and Yin-Chang Ch'u, Shao-Hsun Wang, and Wan-Sen Ma: The Heart in Severe Anemia. Chinese M. J. 52: 479, 1937.

Ten patients suffering from severe anemia (hemoglobin about 2.5 gm. or 17 per cent), without any other discoverable factor that might cause heart disease, were observed for the effects of such anemia on the cardiovascular system, with clinical, radiologic, and electrocardiographic studies. In addition, venous pressure by the direct method and the arm-to-tongue circulation time were determined in most of the cases.

Three patients showed marked cardiac enlargement with little or no evidence of congestive failure. Six showed marked cardiac enlargement and marked congestive failure. One had a normal heart. Cardiac enlargement rapidly disappeared with rest and increase of the hemoglobin towards normal, and the heart assumed normal size and shape when the blood became normal. Diastolic cardiac murmurs encountered in two patients during the height of anemia disappeared with the latter. All patients except one had sinus tachycardia and large pulse pressure.

Six patients presented physical evidence of marked congestive heart failure, including the elevation of venous pressure. The relative duration of electrical systole was prolonged. In spite of elevated venous pressure the circulation time remained normal.

It is concluded that marked cardiac enlargement and marked congestive heart failure may result from prolonged, severe anemia alone, particularly in individuals who have extra demands on their circulatory system (physical exertion, fever, pregnancy, parturition, etc.). Both cardiac enlargement and cardiac failure in such cases disappear rapidly, when the anemia is removed. "Anemia heart" should be considered a clinical entity.

AUTHORS.

Kisch, F.: Sudden Cardiac Death in Angina Pectoris in the Absence of Coronary Thrombosis. Klin. Wchnschr. 16: 708, 1937.

In 13 cases out of 36 of sudden death with angina pectoris, no coronary thrombosis was found. In all of these either syphilitic closure of the mouths of the coronaries or coronary occlusion of the arteries by arteriosclerosis was found. The author considers death as reflex in origin.

KATZ.

Starr, Isaac, Gamble, C. J., Donal, J. S., and Collins, L. H.: Estimations of the Work of the Heart During and Between Attacks of Angina Pectoris. J. Clin. Investigation 17: 287, 1938.

In four cases of cardiac pain, three of them suffering from typical angina pectoris, estimations of cardiac output, basal metabolic rate, blood pressure, pulse rate, and respiration were made during the pain and, under comparable conditions, when the patients were free from it. In one case a necropsy was secured. The changes following relief by nitroglycerin were studied in two cases.

The results indicate that the work of the heart was significantly greater during the pain than when the patients were free from it.

The results are consistent with the widely accepted view that cardiac pain is caused by situations demanding increased cardiac work when the heart's blood supply cannot be increased correspondingly.

AUTHOR.

Graef, Irving, Berger, Adolph R., Bunim, Joseph J., and de la Chapelle, Clarence E.: Auricular Thrombosis in Rheumatic Heart Disease. Arch. Path. 24: 344, 1937.

Certain conditions appear to favor the development of auricular thrombi. These are severe mitral stenosis, together with congestive heart failure, auricular fibrillation, and continued local inflammation. On analysis of these factors, the persistence of active inflammation appears to be the chief one in the light of present knowledge.

The occurrence of fibrin-staining material beneath the endocardium can be differentiated from the focal swelling of collagen in the same structure by the use of Mallory's phosphotungstic acid-hematoxylin stain. The fibrin-staining material thus demonstrated is presumably derived from the proximate blood stream.

AUTHOR.

Schneyer, K.: Pulsus Rarus in Aortic Stenosis. Ztschr. f. Kreislaufforsch. 30: 161, 1938.

Sixteen cases of aortic stenosis were found in 2,851 cases of valvular disease. The heart rate in these cases of aortic stenosis was between 58 and 62 beats per minute. Isthmus stenosis of the aorta has faster rates. The author does not believe this slow rate to be reflex in origin.

KATZ.

Sutton, Lucy Porter, and Dodge, Katharine G.: The Relationship of Sydenham's Chorea to Other Rheumatic Manifestations. Am. J. M. Sc. 195: 656, 1938.

Sydenham's chorea is not usually per se a serious condition.

Rheumatic heart disease develops in approximately 20 per cent of patients who have had chorea as the only clinical manifestation of rheumatic infection.

The child who begins his rheumatic disease with chorea runs a 50 per cent chance of developing heart disease.

The child who begins with chorea runs a 50 per cent chance of developing other rheumatic manifestations later, of if muscle and joint pains are included, a 75 per cent chance. Emotional factors are no more important, and probably less so, in initiating an attack of chorea than preceding acute infection, including rheumatic polyarthritis.

Chorea should continue to be regarded not only as a manifestation, but as a major manifestation of rheumatic infection.

AUTHOR.

Southworth, Hamilton, and Stevenson, Charles Summers: Congenital Defects of the Pericardium. Arch. Int. Med. 61: 223, 1938.

A description is given of a patient showing congenital absence of the left leaf of the parietal pericardium, with an interpleural window in the upper portion of the anterior mediastinum.

This is the first case reported in the literature in which adequate clinical date have been given and in which fluoroscopic examination has been included.

In a survey of the literature forty-five definite instances of this defect have been found, together with seven other instances in monstrous births and two doubtful cases.

Analysis of these cases reveals that the defect was almost invariably on the left; that in 76 per cent of the cases it was so completely on that side that the heart and the left lung were in a common serous cavity; that in 77 per cent of the cases the subject was a male; and that the condition is not incompatible with normal life, having in only one instance been directly responsible for death and having otherwise possibly caused cardiac symptoms in only three cases.

Unexplained cardiac enlargement may occur (in about half the cases), but it is apparently not related to the presence or absence of adhesions.

The chief danger from the defect lies in exposing the heart to pulmonary infection, with death in 27 per cent of the cases, including our own, associated with pleuropericarditis.

Although in no case as yet has the condition been diagnosed ante mortem, this should be possible in some instances on the basis of certain criteria adapted from Maude Abbott.

AUTHOR.

Welper, W.: Hyperergic Thromboendarteritis in the Lungs of Infants in the Presence of Eclampsia of the Mother. Arch. f. Kreislaufforsch. 2: 210, 1938.

In a 3-day-old infant evidence was found of thromboendarteritis in the peripheral arteries of the lung. The changes resemble those seen in allergic disorders and are attributed to the severe eclampsia of the mother, suggesting that eclampsia is allergic in character (?).

KATZ.

Waring, J. I.: Nutritional Heart Disease in Children. Am. J. Dis. Child. 55: 750, 1938.

Nutritional heart disease is not uncommon among negro children in Charleston, S. C. Thirteen cases summarized here suggest that the cardiac changes are due not entirely to a lack of vitamin B but to a rather more general deficiency of dietary materials and that a satisfactory response to dietetic treatment may be expected in cases in which the illness is not too far advanced.

AUTHOR.

Bland, Edward F., and Jones, T. Duckett: Fatal Rheumatic Fever. Arch. Int. Med. 61: 161, 1938.

Since 1921 (sixteen years) approximately 1,500 children and adolescents under the age of 21 years have received hospital care at the House of the Good Samaritan for rheumatic fever and chorea. The subsequent course and present status of this large group are known. We have presented in this report data relevant to the 306 patients who have died. Post-mortem examination was made in 74 instances (24 per cent). From a consideration of this group of patients who have died the following conclusions may be cited:

1. Rheumatic fever has been the outstanding cause of death and was directly responsible for the fatal issue in 250 instances (82 per cent).

2. The early years after the onset of the disease have proved to be a critical period. In approximately half (47 per cent) of the fatal cases death occurred during the first three years and in two-thirds (62 per cent) during the initial five years.

3. Thereafter the extent of residual cardiac enlargement (dilatation) and, to a lesser degree, the rapidity with which it developed have served as the most reliable criteria of the severity of the preceding infection as well as an index of the future susceptibility of the individual patient to subsequent fatal rheumatic fever.

4. The age of the patient at the time of onset of rheumatic fever (or chorea) during the first fifteen years of life has been of no significance so far as subsequent longevity is concerned.

5. The manifestations of fatal rheumatic fever had been stressed and contrasted with the generally accepted clinical picture of the disease.

AUTHOR.

Bruger, Maurice, and Fitz, Fred: Experimental Atherosclerosis: 1. Effect of Prolonged Administration of the Thyrotropic Factor. Arch. Path. 25: 637, 1938.

The feeding of iodine prevents the deposition of cholesterol in the arteries of rabbits fed cholesterol. Thyroidectomy abolishes this protective action of iodine. This striking relationship between experimental atherosclerosis and the function of the thyroid gland led the writers to learn whether the thyrotropic factor, from the pituitary gland, has an effect on experimental atherosclerosis in rabbits (cholesterol-feeding method). The results were as follows: The aortas of cholesterol-fed rabbits contained several times as much cholesterol as normal controls. The aortas of rabbits receiving injections of thyrotropic factor contained about the same amount of cholesterol as normal controls. The aortas of rabbits being fed cholesterol *and* receiving injections of thyrotropic factor contained, on the average, nearly twice as much cholesterol as the cholesterol-fed rabbits not receiving thyrotropic factor. In an attempt to explain these findings some theoretical considerations are discussed.

MONTGOMERY.

Immel, R.: Hemostatic Pressure Rise and the Arterial System. Klin. Wchnschr. 16: 956, 1937.

When a patient stands up, the pressure in the brachial artery increases as a result, so the author states, of an increase in tone of the medium-sized arteries.

KATZ.

Jones, E. Idris: A New Syndrome Apparently Due to Over-Activity of the Posterior Pituitary. Lancet 1: 11, 1938.

A patient in whom hypertension, hyperchromic anemia, achlorhydria and abnormal carbohydrate tolerance were present has been observed over a period of eight months. The fact that in animals it is possible to produce hyperchromic anemia and achlorhydria by injection of posterior pituitary extract suggested that the combination of hyperchromic anemia and hypertension was not fortuitous but that the syndrome might be due to overactivity of the posterior pituitary. An extract with pressor and antidiuretic activity was obtained from the urine of this patient. This was considered additional evidence of hyperfunction of the posterior pituitary. Treatment with liver extract resulted in a return of the blood count and hemoglobin to normal, a more normal carbohydrate tolerance curve, and a fall in the blood pressure to normal levels. It is suggested that this is a new syndrome due to hyperfunction of the posterior pituitary.

HINES.

Bergfeld, W., and Meessen, H.: Hypophysis and Hypertension. Ztschr. f. klin. Med. 132: 283, 1937.

In 8 out of 9 cases of malignant nephrosclerosis with hypertension, examination showed basophylic cellular increase in the hypophysis. This was true also in 8 out of 9 cases of hypertension with chronic nephritis. It was absent in 4 cases of acute and subacute nephritis. It was found in only 2 out of 50 controls.

KATZ.

Turner, Roy H.: Studies in the Physiology of Blood Vessels in Man: Apparatus and Methods: I. A Sensitive Plethysmosphygmograph for a Portion of the Finger. J. Clin. Investigation 16: 777, 1937.

An apparatus designed particularly for measuring volume changes due to the state of fullness of the blood vessels of a sharply defined portion of the human finger is described as to construction, mode of operation, and working characteristics. The apparatus makes a graphic record of pulse volumes as small as 0.1 c.mm. and of gradual volume changes as great as 1,000 c.mm. The pulse recorder, which employs an optical capsule in which stretching of the rubber membrane is largely avoided, shows high sensitivity, low moving mass, responds well to volume changes at a frequency up to 40 cycles per second and with diminished amplitude to 60 cycles per second, and is well damped. The apparatus and method interfere to a minimum with the body part under study except through undesirable temperature and humidity of the air in contact with the skin.

AUTHOR.

Sodeman, W. A.: Studies in the Physiology of Blood Vessels in Man: Apparatus and Methods: II. A Method for the Determination of the Volume of the Soft Tissue About the Terminal Phalanx of the Human Finger. J. Clin. Investigation 16: 787, 1937.

This communication deals with the method for estimating in the living human being the volume of soft tissue in that portion of the finger which, for lack of a better term, is called the finger tip.

The method consists of a determination of the total volume of the finger tip, an estimation of the bone volume, and a calculation of the soft tissue volume by difference. The finger tip has been defined in terms of skin markings as that portion of the finger distal to a plane passing through the center of the dorsal and palmer skin crease at the distal interphalangeal joint. This plane passes through the distal end of the second phalanx.

MCCULLOCH.

Turner, Roy H., Burch, George E., and Sodeman, William A.: Studies in the Physiology of Blood Vessels in Man: III. Some Effects of Raising and Lowering the Arm Upon the Pulse Volume and Blood Volume of the Human Finger Tip in Health and in Certain Diseases of the Blood Vessels. J. Clin. Investigation 16: 789, 1937.

Changes in total blood volume and pulse volume of the finger tip due to elevation and depression 45 cm. from heart level for a group of males including normal subjects and patients suffering from various vascular abnormalities are reported and discussed.

Pulse volume increased with elevation and decreased with depression of the finger tip, and total volume changed in the opposite direction. The adaptive mechanisms are discussed in terms of behavior of various vessel groups.

The influence of position upon pulse volume is ascribed to change in distensibility of both arterial and venous vessels and to changes in frictional resistance to blood flow and consequent changes in smoothing effect on the pulse wave which are predominantly arterial.

AUTHORS.

Rubenstone, Abraham I.: Postoperative Circulatory Collapse Accompanied by Acidosis. Pennsylvania M. J. 41: 673, 1938.

Vascular changes rather than the heart are involved in postoperative circulatory collapse. Chemical imbalances may further aggravate the patient's condition. Four cases are presented. In all four the alkali reserve was between 25 and 36. Three of the patients recovered, and in them the alkali reserve returned to normal or nearly to normal. Treatment advised consists of blood transfusions, oxygen tent, water, chloride, or Ringer's solution and strychnine, pitressin, ephedrine, and adrenalin. In acidosis buffer solutions, such as Hartmann's, are indicated. Digitalis is of secondary importance.

MONTGOMERY.

Budelmann, G.: Cardiac Pulmonary Congestion in Practice. Deutsche med. Wchnschr. 63: 1105, 1937.

Congestion in the lung occurs when the left heart does not pump out the blood pumped into the lungs by the right heart. This interferes mechanically with the expansion of the lungs, decreases vital capacity, and so explains the sense of chest oppression in many of these patients. It may cause dyspnea with or without evidence of interference of gaseous exchange in the lungs. The x-ray demonstrates only extreme forms of congestion although the end results of milder chronic forms may appear as induration and bronchial involvement. In treatment, two principles are important: viz., improve the power of the left heart and decrease the venous return to the right heart.

KATZ.

Gibson, John G., and Evans, William A., Jr.: Clinical Studies of the Blood Volume. III. Changes in Blood Volume, Venous Pressure, and Blood Velocity Rate in Chronic Congestive Heart Failure. J. Clin. Investigation 16: 851, 1937.

In heart disease the change from the compensated to the decompensated state is accompanied by a progressive increase in the volume of plasma and red cells.

This increase is shared to a slightly less extent by the plasma than by the corpuscles, resulting in a slight concentration of the blood.

The average degree of increase in blood volume above normal parallels the average degree of elevation of venous pressure and slowing of circulation time.

During recovery from congestive failure there is a diminution in both plasma and cell volume, the degree of decrease in plasma in most cases being at first more rapid than that of the corpuscles, resulting in varying degrees of blood concentration. With continued compensation the proportion of cells to plasma returns to within normal limits. The decrease in total volume parallels the degree of clinical improvement.

In no case was an increase in volume during recovery from chronic congestive failure observed. Relapses to more severe degrees of circulatory failure are accompanied by maintained elevation of, or further increases in, blood volume.

AUTHORS.

Thomson, William A. R.: The Organic Mercurial Diuretics in the Treatment of Cardiac Oedema. Quart. J. Med. 6: 321, 1937.

The therapeutic value of the various organic mercurial diuretics, known by the trade names of salyrgan, neptal, novurit, mersalyl, and novurit suppositories, has been investigated in 66 patients, 61 of whom had congestive heart failure with edema. Of these, 33 had auricular fibrillation, and 28 had normal rhythm.

The average twenty-four-hour excretion of urine per intravenous injection of 2 c.c. was for salyrgan 2,670 c.c. (94 oz.), for neptal 2,670 c.c. (94 oz.), for mersalyl 2,860 c.c. (101 oz.), and for novurit 3,000 c.c. (105 oz.).

The intramuscular route was seldom employed, but of 18 injections of neptal, 9 were intramuscular and 9 were intravenous. The average twenty-four-hour diuresis per injection was 2,670 c.c. (94 oz.) for the intravenous group and 2,190 c.c. (77 oz.) for the intramuscular group.

Mercurial (novurit) suppositories were successfully employed on 208 occasions with an average diuresis per suppository of 2,360 c.c. (83 oz.).

Almost without exception the administration of ammonium chloride, 60-90 grains (4-6 gm.) daily, for the two or three days preceding and on the day of the administration of the mercurial diuretic, resulted in an increased diuresis.

The administration of digitalis had no appreciable effect upon the diuretic response to the mercurial diuretics. Even when patients with auricular fibrillation were separately considered, the diuretic response was little affected by digitalis.

No serious toxic effects were observed during this investigation.

The organic mercurial diuretics are safe and efficient and have an almost universal application in the treatment of cardiac edema. There is little to choose between the various preparations now available, except that those containing theophyllin are rather more active.

The dose, either intravenous or intramuscular, is 2 c.c. of the solution as supplied by the manufacturers. The intravenous route is preferable. Two clear days should elapse between the injections (or the suppositories). Preliminary small doses are not required. If local conditions preclude the use of an undiluted injection, it is better to make use of the suppositories.

Mercurial (novurit) suppositories are satisfactory and easily administered, though the resulting diuresis is less than from an injection. They should, when possible, be preceded by an aperient two nights before or by an enema a few hours before.

The optimum dosage of ammonium chloride is 20-30 grains (1.3-2 gm.) thrice daily, i.e., 60-90 grains (4-6 gm.) daily, for two or three days preceding, and on the day of, the administration of the mercurial diuretic. For practical purposes this means continuous administration when the mercurial preparation is being given regularly on every third day (i.e., with two-day intervals).

Mercurial diuretics appear to act as efficiently in dispersing edema whether digitalis is being given or not, although digitalis is generally indicated and should be given because of the failure. Indeed, the mercurial diuretics should take precedence even over digitalis where edema is the prominent feature in congestive failure. Hydrothorax or ascites, as well as anasarca, will respond to these preparations, which should make the use of paracentesis, skin puncture, or Southey's tubes a rare necessity. Where there is cardiac asthma, orthopnea, and enlargement of the liver—yet without external edema—they should be used; and for incipient heart failure they find a place with digitalis in preventing the onset or recurrence of edema.

AUTHOR.

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Original Communications

THE ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC DIAGNOSIS OF CORONARY DISEASE

A COMPARATIVE STUDY OF 140 CASES*

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BOSTON, MASS.

THE purpose of this paper is to present the roentgenologic criteria for the diagnosis of coronary disease, principally occlusion, and to compare, in a larger series of cases than was available at the time of our previous communications,[1, 2] the results of this method with the results obtained by electrocardiography. The report is based on 140 cases in which an attempt was made to establish the diagnosis by roentgenologic means alone, without knowledge of the history, physical findings, or electrocardiogram. Necropsies were performed in 12 of these cases.

Roentgenographically, the left border of the heart as seen in the frontal position is formed by the anterolateral wall of the left ventricle, which extends from the auriculoventricular sulcus to include the apex (Fig. 1). At the upper extremity of this border a variable portion of the left auricle is visible. The part formed by the left ventricle may be considered as an arc subtended by the auriculoventricular and interventricular sulci. Its convexity depends on the mass and tone of the muscle. The effect of abnormal thickness of the myocardium on the contour of the left border is exemplified in chronic hypertension and aortic stenosis, and the influence of muscle tone is due to the fact that the greater the tone, the shorter and thicker the fibers.

The thickness of the left ventricle may be measured by joining the auriculoventricular sulcus and the apex, and erecting thereon a perpendicular from the point of greatest salience of the left ventricular

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curve. This perpendicular (bisector) is a good approximation to the thickness of the myocardium.[3, 4]

ROENTGENOLOGIC DIAGNOSIS

The roentgenologic diagnosis of coronary disease depends more on careful fluoroscopic examination than on inspection of the teleoroentgenogram. It is our practice to time, with a stop watch, the duration of twenty beats of the auricles and ventricles. By this means it is often possible to detect disturbances in the mechanism of the heartbeat which, according to accepted clinical criteria,[5, 6] are strongly suggestive of coronary disease (e.g., A-V heart block, Figs. 2, 3, and 13). It is noteworthy that the average normal heart rate on fluoroscopic

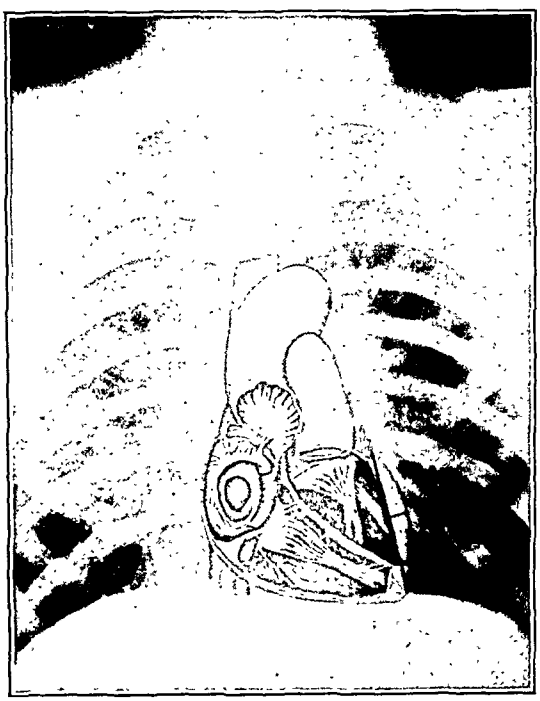

Fig. 1.—The left border of the heart is formed by the left ventricle, the thickness of which is shown by joining the apex and auriculoventricular sulcus.

examination is 100 a minute; this tachycardia is undoubtedly due to apprehensiveness and the lugubrious air of the fluoroscopic room. A rate of 50 or 60 will therefore arouse immediate suspicion, indicating the need for careful investigation.

After the rate has been counted, the systolic-diastolic excursion of all parts of the heart and great vessels is studied. *In coronary occlusion there is a localized diminution of this excursion.* This is best recognized by comparison with the movement of adjacent parts of the cardiovascular shadow, namely, the left auricle and ascending aorta. Although the entire heart may show diminished activity, the greatest change will be observed in the area of infarction. It is necessary to distinguish between active muscular contraction along the entire left

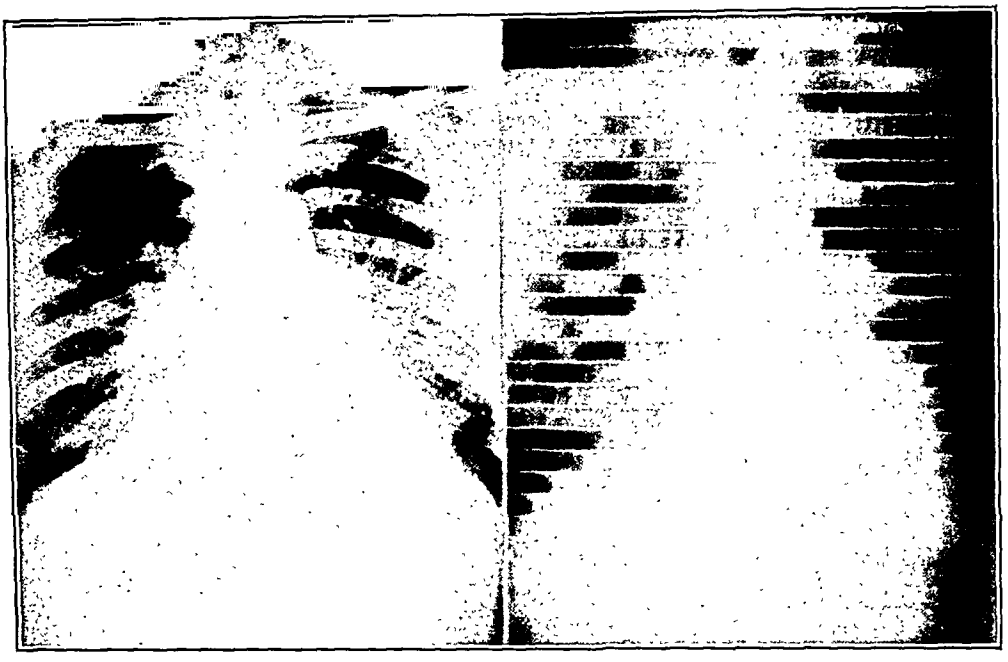

Fig. 2. Fig. 3.

Fig. 2.—Coronary thrombosis. There is a loss of convexity of the left border of the heart, and the heart showed diminished amplitude of pulsations under the fluoroscope. Male, aged 54 years, complaining of constricting sensation in chest, pain in left chest radiating to arm, and vomiting.

Fig. 3.—Kymogram, same case as in Fig. 2. Note marked diminution of amplitude in area included in brackets.

Fig. 4.—Coronary thrombosis showing loss of convexity of left border. The heart appears to "sag." Fluoroscopically there was marked decrease in the amplitude of pulsations. Male, aged 68 years, complaining of dyspnea, pain in chest, orthopnea of seven weeks' duration. Similar attack twelve years earlier. Attacks every three months growing more severe. Pain stopped suddenly three days before examination. Electrocardiogram was consistent with coronary thrombosis.

border and motion due to "dragging" of a portion of the shadow by unaffected adjacent heart muscle.

Inspection of the contour of the left heart border will usually show a loss of convexity, probably because of diminished muscle tone and involutionary changes in the myocardium. In the teleoroentgenogram the left border may be straight or concave (Fig. 4). The right and left median diameters lie almost in the same plane, close to the diaphragm. The heart often appears to sag. The thickness of the left ventricle, as measured by the bisector, is reduced. In most instances, unless there is an associated valve lesion or hypertension, the heart is not enlarged, but in cases of acute coronary occlusion the transverse

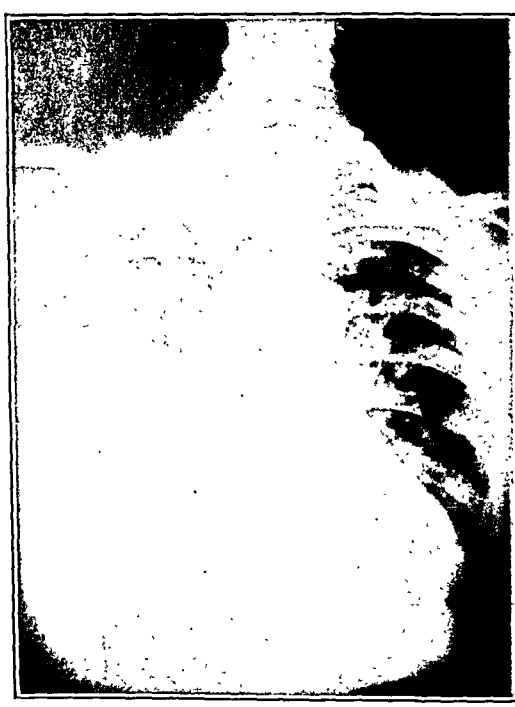

Fig. 5.

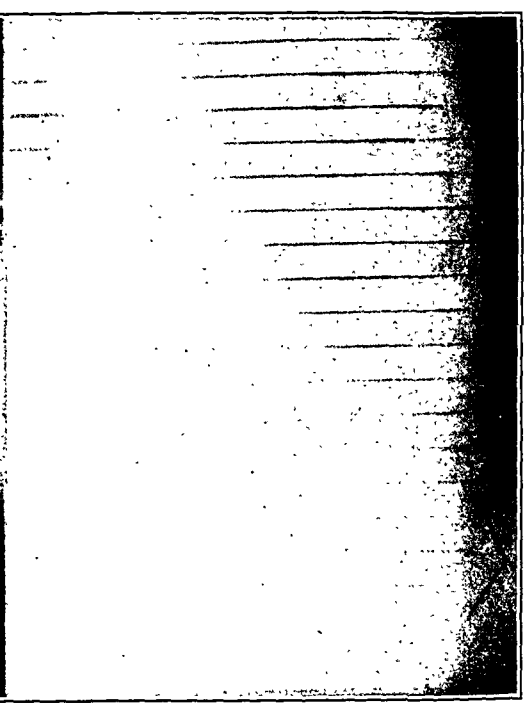

Fig. 6.

Fig. 5.—Coronary thrombosis, acute. There is a loss of convexity of the left border with an increase in the transverse diameter of the heart. Free fluid in pleural cavity and congestive infiltration of the lungs. Fluoroscopic examination showed marked diminution of amplitude. Male, aged 56 years, complaining of dyspnea, palpitation, fatigue, edema, and ascites. Previous cardiac pain. Died one week after examination. Electrocardiogram was consistent with coronary thrombosis.

Fig. 6.—Kymogram, same case as in Fig. 5. Note absence of pulsations in region of left ventricle.

diameter of the heart increases, signifying myocardial insufficiency and congestive failure which are presumably due to inadequacy of the collateral circulation. (Figs. 5, 6, and 13.)

The fact that loss of convexity of the left border is not a constant roentgenographic feature of myocardial infarction is illustrated by Fig. 7. In such cases a diagnosis is obviously impossible unless fluoroscopic examination or a roentgenkymogram (Figs. 8 and 13) shows localized diminution of the ventricular contractions. In our opinion,

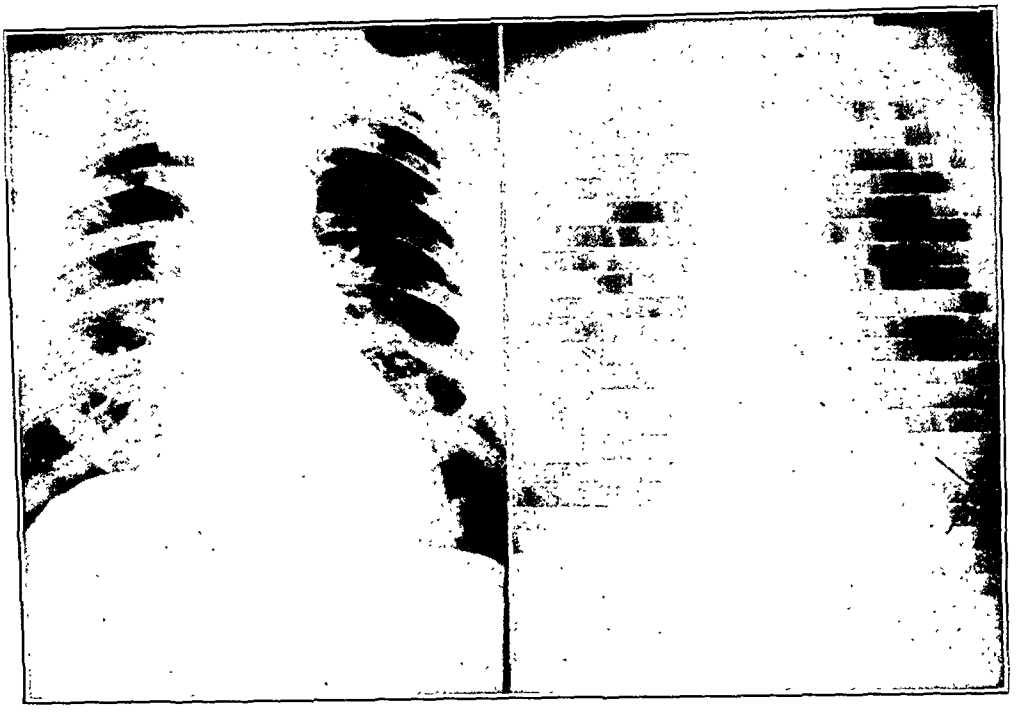

Fig. 7. Fig. 8.

Fig. 7.—Coronary thrombosis. The heart contour shows no recognizable departure from normal. Diagnosis depends upon seeing diminished amplitude of ventricular contractions under the fluoroscope. Male, aged 60 years, no history of symptoms referable to heart. Electrocardiogram was consistent with coronary thrombosis.

Fig. 8.—Kymogram, same case as in Fig. 7, showing marked diminution of ventricular contractions.

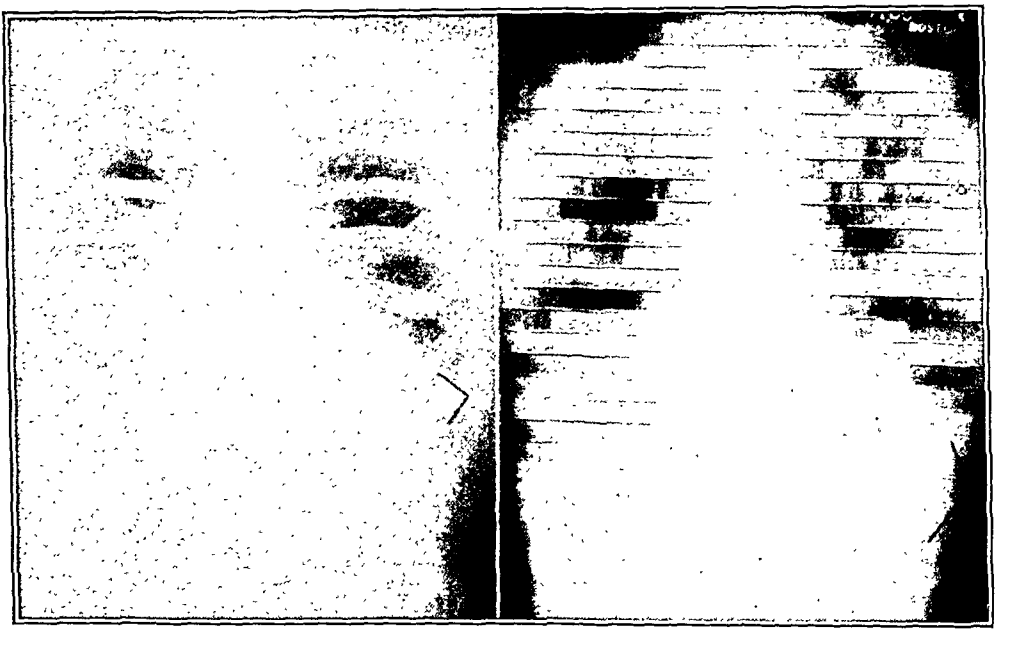

Fig. 9. Fig. 10.

Fig. 9.—Coronary thrombosis in a case of chronic hypertension. Note hypertrophy of the left ventricle due to hypertension and the area of localized flattening (brackets) due to infarction. The latter region showed a marked localized diminution of amplitude. Female, aged 44 years, complaining of dyspnea, orthopnea, and hemiplegia. Blood pressure, 224/140. Electrocardiogram was consistent with coronary thrombosis.

Fig. 10.—Kymogram, same case as in Fig. 9. Note absence of pulsations in lower portion of left ventricle, corresponding to area of infarction shown in Fig. 9,

loss of convexity is dependent not only on the extent of the area involved, but also on the thickness and tone of the myocardium and the time required to develop more or less complete occlusion.

When coronary occlusion occurs in a patient with hypertension, the smooth curve characteristic of hypertension is interrupted by an area of flattening (Figs. 9, 10, 13), and, under the fluoroscope, the amplitude of contractions in this region is seen to be diminished.[7] Inasmuch as the amplitude of contractions in hypertension is increased, this localized diminution is not as marked as it would have been without the antecedent hypertension, but it is just as conspicuous relatively.

Fig. 11. Fig. 12.

Fig. 11.—Narrowing of coronary ostia in a case of syphilitic aortitis. The heart itself shows no alteration in size or contour. There was definite diminution of the amplitude of cardiac contractions indicating myocardial disease. Male, aged 48 years, complaining of dyspnea, fatigue and pain in the chest. Kahn and Wassermann reactions, positive. Electrocardiogram was consistent with coronary thrombosis.

Fig. 12.—Kymogram, same case as in Fig. 11. Note diminished amplitude in region of lower left ventricle.

Our chief difficulty has been in distinguishing between coronary disease and pure hypertensive failure. The diagnosis is also difficult in the presence of valvular disease, for, although one can readily determine by fluoroscopic examination that there is a myocardial lesion, it is frequently impossible to decide whether it is due to inflammatory or syphilitic change, or to superimposed coronary occlusion (Figs. 11, 12, 13).

By means of the roentgenkymogram it is possible to make a permanent record of the abnormalities of cardiac contraction which are observed under the fluoroscope. Kymographic studies by Scott and

Moore,[8] Stumpf,[9, 10] and others[11] have confirmed our observations relative to the localized diminution in the amplitude of contractions. Fig. 13 illustrates such a diminution. The kymogram, however, useful as it is, does not eliminate the need for careful fluoroscopic examination, for the usual horizontal slit kymogram records only the mediolateral component of motion, and, inasmuch as the mediolateral movement of the apex of the heart is usually less than the cephalocaudal, such a kymogram is likely to show a loss of excursion in this area which might be misinterpreted if no fluoroscopic examination were made.

The validity of these diagnostic criteria is shown in the accompanying tables, which include only those cases in which electrocardiograms were available for comparison. Patients who were too ill to be moved to the x-ray department for fluoroscopic examination were not in-

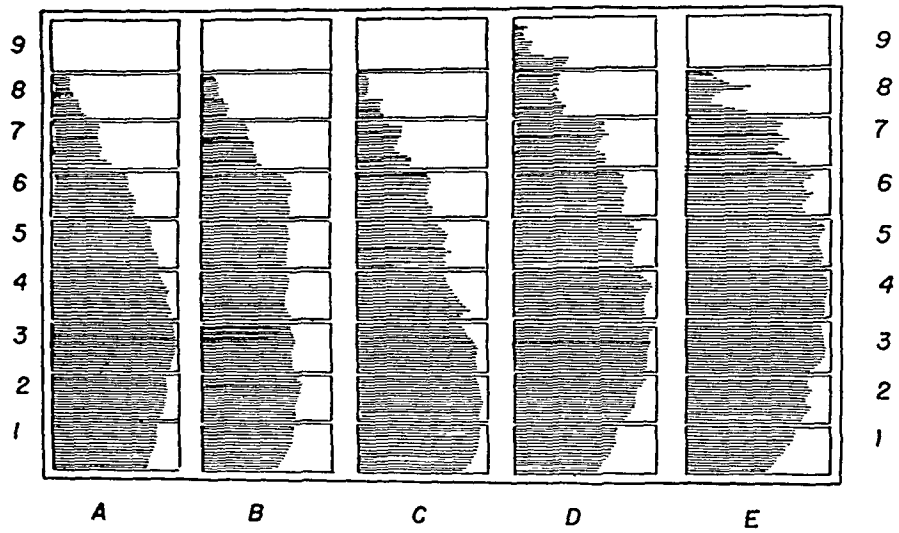

Fig. 13.—Tracings of kymograms showing details of left ventricular contractions: *A*, Fig. 3; *B*, Fig. 6; *C*, Fig. 8; *D*, Fig. 10; *E*, Fig. 12. Compare waves with normal beat in frame *8E*.

cluded. A few acutely ill patients were referred with divers clinical diagnoses, such as cholecystitis, pneumonia, and gastric ulcer. In each case the diagnosis of coronary disease was first established by roentgenologic examination. Of 140 cases in which a roentgenologic diagnosis of coronary disease was made, confirmatory electrocardiograms were obtained in 103, or 75.7 per cent (Table I). (Four cases in this series were excluded because previous administration of digitalis interfered with the interpretation of the electrocardiograms.) The electrocardiograms, which included Lead IV, were reviewed by Dr. William D. Reid and Dr. Maurice A. Lesser, of the Massachusetts Memorial Hospitals, and Dr. Howard B. Sprague, of the Massachusetts General Hospital.

In a small series of 10 cases in which roentgenologic examination was made because of pain in the chest, we found no recognizable dis-

ease of the heart, and the electrocardiograms were negative in each of these cases—a correlation of 100 per cent. This small additional series is presented as a check on the negative diagnosis by roentgenologic examination.

Table II shows a group of 12 autopsied patients who had been examined both roentgenologically and electrocardiographically. The roentgenologic diagnosis was confirmed in 10 cases, or 83.3 per cent,

TABLE I

CASES IN WHICH A DIAGNOSIS OF CORONARY DISEASE WAS MADE BY ROENTGENOLOGIC EXAMINATION

Number of cases	140
Confirmatory electrocardiograms	103
Electrocardiograms not in agreement with roentgenologic findings	33
Cases excluded; electrocardiograms equivocal (digitalis)	4
Percentage confirmation	75.7

TABLE II

ROENTGENOLOGIC, ELECTROCARDIOGRAPHIC AND NECROPSY FINDINGS IN 12 CASES

NO.	ROENTGENOLOGIC DIAGNOSIS	ELECTROCARDIOGRAM	AUTOPSY
1	Coronary thrombosis	Suggestive of coronary thrombosis	Myocardial fibrosis, coronaries show marked intimal thickening
2	Coronary thrombosis	Coronary thrombosis	Sclerosis and occlusion of coronary arteries, myocardial fibrosis
3	Coronary thrombosis, left descending branch	Myocardial disease	Occlusion of left anterior descending branch
4	Coronary thrombosis	Coronary disease	Scarring and fibrosis, hyalinization of left ventricle, occlusion of anterior descending branch
5	Coronary thrombosis	Myocardial impairment	Diffuse scarring, hyalinization of myocardium, marked coronary sclerosis and narrowing
6	Coronary thrombosis	Coronary thrombosis	Myocardial fibrosis, coronaries fibrotic, irregular ostia, intimal thickening
7	Coronary thrombosis	Coronary occlusion	Infarct, complete occlusion of anterior descending branch
8	Acute coronary thrombosis	Acute coronary thrombosis	Myocardial fibrosis, recent coronary occlusion
9	Hypertension with failure	Hypertension, myocardial infarct	Infarct, left ventricle (posterior)
10	Heart negative	Recent coronary disease	Infarct at apex, coronary sclerosis
11	No evidence of organic heart disease	Coronary thrombosis	Heart and coronary arteries negative, bilateral pulmonary thrombosis
12	Coronary thrombosis	Coronary thrombosis	Myocardial fibrosis, infarction

and the electrocardiographic diagnosis in 11 cases, or 91.7 per cent. In Case 11 the electrocardiogram was consistent with coronary occlusion, but the heart was reported negative on roentgenologic examination. Autopsy showed bilateral primary pulmonary thrombosis, but no disease of the heart or coronary arteries.

DISCUSSION

It is our belief that roentgenologic examination of the heart in cases of suspected coronary disease is an important adjunct to the other diagnostic methods which are generally employed. Moreover, it is our opinion that an accuracy of 75.7 per cent as judged electrocardiographically does not indicate the true value of roentgenologic examination. Schlesinger[12] points out that autopsy shows varying degrees of narrowing of the coronary arteries in many patients who gave no history of angina and had normal electrocardiograms. We have been able to make a roentgenologic diagnosis of coronary disease in numerous cases in which, in spite of a definite history of coronary attacks, the electrocardiogram was normal. It is obvious that the electrocardiogram portrays electrical variations which do not necessarily parallel changes in the physical activity of the heart muscle. Stumpf[10] records numerous instances in which, although the electrocardiogram was negative, the roentgenkymogram showed definite evidence of coronary disease and the diagnosis was confirmed both by the history and necropsy. Sprague and Orgain,[13] in a series of proved cases of coronary disease, also found numerous instances in which the electrocardiogram failed to give positive information. Kennedy,[14] in a review of 200 cases in which autopsies were performed, mentions the absence of a history of pain in 22 per cent of "old" cases and in 4 per cent of "recent" cases of coronary occlusion. Thus it is apparent that the results of roentgenologic examination in coronary disease cannot be invalidated because they do not agree exactly with those obtained by other methods which are themselves subject to a variable factor of error. It is known that cardiac infarction may occur without graphic evidence[15] and that the electrocardiogram may return to normal after the patient has recovered from his coronary occlusion, but in either case there are permanent structural changes in the heart muscle which may possibly be detected by other methods of examination. Again, the use of digitalis may so alter the electrocardiogram as to render it useless in the diagnosis of coronary disease, but the physical changes upon which the roentgenologic diagnosis is based are not affected by this drug.

SUMMARY AND CONCLUSIONS

The roentgenologic diagnosis of coronary disease is based on careful fluoroscopic examination as well as on study of the teleoroentgeno-

gram. By these means it is possible to detect alterations in the contour and activity of the heart. In a series of 140 cases in which the diagnosis of coronary disease was made by roentgenologic examination without knowledge of the history, physical findings, or electrocardiograms, confirmatory electrocardiograms were obtained in 75.7 per cent. In an additional series of 10 cases of pain in the chest, roentgenologic examination showed nothing and the electrocardiograms were normal—a correlation of 100 per cent. Of 12 cases in which both roentgenologic examination and electrocardiograms were made, necropsy confirmed the roentgenologic diagnosis in 10, or 83.3 per cent, and the electrocardiographic diagnosis in 11, or 91.7 per cent.

Roentgenologic examination is a valuable adjunct in the diagnosis of coronary disease, and we feel that it should be employed in every case in which the physical condition of the patient permits. It not only affords confirmatory evidence, but furnishes additional objective information pertaining to associated cardiac lesions and pulmonary complications. It is, moreover, useful in detecting coronary disease when the electrocardiographic changes have not yet developed or have already disappeared.

In appreciation of the assistance given us in this study we wish to express our sincere thanks to Dr. William D. Reid, Dr. Howard B. Sprague, and Dr. Maurice A. Lesser.

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INFLUENCE OF CERTAIN GLUCOSIDES OF DIGITALIS LANATA ON THE CORONARY BLOOD FLOW AND BLOOD PRESSURE IN THE TRAINED DOG*

HIRAM E. ESSEX, PH.D., AND J. F. HERRICK, PH.D., ROCHESTER, MINN. AND MAURICE B. VISSCHER, PH.D., M.D., MINNEAPOLIS, MINN.

FROM a practical point of view the question whether digitalis bodies constrict the coronary arteries is of considerable importance. If therapeutic doses of digitalis were found to have such an action, the use of this drug in the presence of coronary sclerosis might be contraindicated. The evidence on this point is decidedly conflicting. The earlier work is cited by Cushny[1] (1925), Gilbert and Fenn[2] (1932), and Weese[3] (1936).

The effect of digitalis on the coronary vessels has been studied by a variety of methods and with many different preparations of the drug. The response of isolated strips of arteries and that of the vessels of the isolated heart to varying doses of digitalis has been investigated; and considerable data have been gathered with the aid of the Morawitz cannula, by means of which the effect of the drug on the outflow from the coronary sinus has been studied both in the intact animal and the heart-lung preparation. When the Morawitz cannula is used, inferences must be made as to the flow in the coronary arteries, and it would be preferable actually to measure the flow. For this purpose three methods are available: 1. The hot-wire anemometer of Anrep and Downing[4] (1926) has certain advantages over other methods. It is easy to calibrate in terms of absolute flow, and gives indications of changes within the cardiac cycle. It can only be used under somewhat artificial conditions, so that the results obtained must be interpreted very carefully. 2. The differential manometer of Wiggers and Cotton[5] (1933) indicates changes in flow, but does not measure absolute quantities. These two methods are easily applicable only to the anesthetized animal with an open thorax, so that artificial respiration must be used. 3. The modification of the Rein[6] (1931) thermostromuhr (Baldes and Herrick,[7] 1937), previously employed by Essex, Herrick, Baldes, and Mann[8] (1936), permits accurate measurement of changes in the mean blood flow through an intact coronary artery without general anesthesia. In this investigation we have used the third method in order to imitate conditions in man as closely as possible.

Numerous preparations of digitalis suitable for intravenous administration are available, but we were interested primarily in the native

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glucosides, since these are of greatest practical importance. Also, it seemed desirable to study single substances rather than mixtures. We therefore made use of the three digilanids, A, B, and C, which were isolated by Stoll and Kreis[9] (1933) from *Digitalis lanata*, and are the only purified native glucosides available.

METHODS

A thermostromuhr unit was placed on the circumflex branch of the left coronary artery in six dogs. After the animals recovered from the anesthetic and the immediate effects of the operation, observations were made at intervals for as long as a week. Before operation, the dogs had been trained to lie quietly on a table for periods of two hours or more. Control measurements of coronary blood flow were made over periods of from thirty minutes to an hour.

After the flow became constant, solutions of a glucoside* were injected into one or another of the superficial veins of the leg, and the effects were noted. Various quantities were injected in different experiments. The amount was from 3 to 50 per cent of the calculated lethal dose, as previously determined by intermittent injection into anesthetized animals. In the experiments reported here, not more than one injection was made in twenty-four hours, and, with the quantities employed, no qualitative differences were observed in the effects of injections on successive days. This is in accord with previous observations that digitalization with divided doses of digiglusin (Lilly) produces no significant change in coronary blood flow in the dog.[21]

RESULTS

The observations are summarized in Table I. All of the dogs weighed between 10 and 12 kg. The average lethal dose for digilanid A is 0.40 mg. per kilogram of body weight; for digilanid B, 0.60 mg.; and for digilanid C, 0.35 mg. It was found that 15 per cent of the lethal dose of digilanid A was without effect on the coronary flow. Larger doses produced nausea, retching, and vomiting, which in themselves result in marked circulatory disturbances that affect the coronary flow profoundly, making interpretation of the specific effect of larger doses of the drug impossible. Consequently, uncomplicated results were not obtained with more than 20 per cent of the lethal dose of any of the digilanids. With digilanid B, less than 10 per cent of the lethal dose produced no change in flow, and 18 per cent or more produced vomiting. In the case of digilanid C, smaller doses were employed because this glucoside is more active in raising cardiac efficiency. Seven injections of less than 17 per cent of the lethal dose were given without measurable change in coronary blood flow except in two instances, an increased flow following the injection in one case and a decreased flow in the other. In both of these instances the dogs had fallen asleep when the change occurred. Whether this was responsible for the observed changes in coronary blood flow we cannot say. In view of the

*We are indebted to the Sandoz Company, Inc., for supplies of the glucosides employed.

fact that, following five injections in which the dogs remained awake, there was no change in coronary flow, it seems safe to ignore these two experiments and to conclude that digilanid C in subnauseating doses does not produce measurable changes in the mean coronary blood flow. Since less than nauseating doses are used in clinical practice, the larger doses whose effects cannot be determined satisfactorily on the trained animal are of little importance except as indicating the level of dosage at which toxic manifestations appear.

TABLE I

EFFECT OF DIGILANIDS A, B AND C ON CORONARY BLOOD FLOW IN TRAINED DOGS

DOG NO.	DATE OCT.	DOSE MG.	EFFECT ON CORONARY BLOOD FLOW	CONDITION OF ANIMAL†
		*Digilanid A**		
1	22	0.50	No change	
2	20	0.60	No change	
3	13	0.60	No change	
		*Digilanid B**		
4	27	0.33	No change	
4	28	0.33	No change	
1	23	0.50	No change	
		*Digilanid C**		
5	8	0.07	No change	
5	9	0.10	18% decrease	Fell asleep
3	15	0.25	Marked increase	Fell asleep
6	8	0.28	No change	
5	11	0.47	No change	Vomited once
5	12	0.47	No change	
6	9	0.60	No change	Vomited once

*Observations on coronary blood flow following larger doses were complicated by circulatory disturbances resulting from nausea and vomiting.

†Unless otherwise noted the animals were resting quietly but were not sleeping.

A single experiment with K-strophanthin showed no effect on the coronary blood flow.

In anticipation of the question whether the method used is suitable for detecting decreases and increases in coronary flow had they occurred following injections of the glucosides, we performed control experiments with pitressin (Parke-Davis) and epinephrine. An intravenous injection of 0.05 c.c. of pitressin caused a large and prolonged decrease in the coronary blood flow, and 0.1 c.c. of a 1:1000 solution of epinephrine given intravenously resulted in a marked increase.

Subnauseating doses of the digilanids do not produce significant changes in arterial blood pressure. With the technic of Hamilton and his associates, two observations were made on the blood pressure of the dog with each of the three digilanids. This point is of importance because doses which raise the blood pressure might easily decrease coronary flow in systole and increase it in diastole (Anrep,[11] 1936).

COMMENT

Some workers have found that perfused arterial strips respond to digitalis by contracting, but one observer reported that relaxation occurred.

The use of the isolated perfused heart has also led to inconsistent results. Rabe[12] (1912) observed that g-strophanthin in a concentration of 1 part per 1,000,000 produced a decrease in the outflow from the coronary arteries only if there was a marked increase in cardiac contraction. The compressing effect of the muscular contraction, which Anrep and Häusler[13] (1928) showed to be a general phenomenon independent of drug action, might account for such decreases in coronary flow. The recent work of Sakui[14] (1935) confirms the earlier work of Rabe, with the additional observation that very small doses increased the flow.

Experiments by Bodo[15] (1928) with the heart-lung preparation seemed to show coronary dilatation following the administration of digitalis. Fisher, Guggenheimer, and Müller[16] (1928) made similar studies, using strophanthin in doses of 0.05 to 0.25 mg. per 500 c.c. of blood in the heart-lung circuit, and found that there was no change with the smaller doses but that larger doses resulted in a decreased coronary flow. The larger doses were in the fatal dose range. Rühl and Wiehler[17] (1934) found that strophanthin had variable effects on coronary sinus outflow in the heart-lung preparation.

In the study of coronary flow in the intact animal several methods have been employed. Meyer[18] (1912) passed a cannula into a superficial coronary vein and measured the outflow. He noted an increase subsequent to the injection of digitalis. Such a method gives no more than a suggestion as to the effect on the total coronary flow. Sakai and Saneyoshi[19] (1915) collected the coronary sinus blood in anesthetized cats with a Morawitz cannula. They found that a single fatal dose of strophanthin (about 0.2 mg.) produced initially a decided fall in the coronary sinus outflow. This occurred in spite of a considerable increase in blood pressure, which would be expected to augment coronary flow. Small doses, such as 0.01 mg., of strophanthin produced a slight increase in coronary flow. This, however, does not necessarily imply a special action on the vessels of the heart, because in these instances also there was an elevation in blood pressure. The authors concluded that doses comparable to those used therapeutically had no specific action on the coronary vessels.

Gilbert and Fenn[2] (1932) likewise collected the coronary sinus blood in dogs. They injected various preparations of digitalis intermittently, using one-tenth of the calculated lethal dose intravenously every ten minutes until the lethal dose was reached. A whole-leaf preparation was employed. One injection of this preparation produced an average

decrease in coronary flow of about 5 per cent. With a third preparation of digitalis they did not find evidence of any coronary constriction. With injections of ouabain they obtained no decisive changes. Vagotomy or atropinization abolished the coronary constriction observed with the whole-leaf preparation.

Three major difficulties present themselves in the interpretation of the work previously reported: 1. The doses of the drug employed when decreases in coronary flow occurred were frequently above the therapeutic range. 2. The observations were made either on isolated or nonworking hearts or on anesthetized animals with open thoraxes, so that artificial respiration was necessary. The circulatory conditions are hardly normal in such experiments. 3. The Morawitz cannula does not measure the total flow from the coronary arteries, but only the portion of the total outflow that escapes the Thebesian veins. We are aware of no experiments showing that the proportion of the total coronary outflow which reaches the sinus is unchanged following the administration of drugs. On the contrary, Anrep, Blalock, and Hammouda[20] (1929) have shown that, with the alteration in the condition of the heart muscle which accompanies progressive spontaneous failure, there is as much as a 30 per cent change in the proportion of the coronary blood which escapes through the sinus.

Since changes in blood pressure did not occur following the injection of subnauseating doses of the digilanids, it may be inferred that these preparations were without peripheral vasomotor effects, but even if the blood pressure had increased, it is probable that the effect on coronary blood flow would not have been unfavorable. According to Anrep[11] (1936), large increases in intraventricular pressure due to increased peripheral resistance would be expected to decrease coronary blood flow in systole and to increase it in diastole, but the net effect would be an increase.

Previous work, to which reference has already been made,[21] and the present investigation seem to show that digitalis and digitalis glucosides have little effect on the coronary blood flow of the trained dog when the drug is given in single or divided doses no larger than those used therapeutically.*

SUMMARY AND CONCLUSIONS

In thirteen experiments, several of the pure, native glucosides of *Digitalis lanata* were injected into dogs in doses smaller than those which will produce retching and vomiting, and the effect on the mean blood flow through the circumflex branch of the coronary artery was measured. In eleven experiments no change was noted; in one experiment there was an increase; and in one, a decrease.

*In a recent paper W. B. Kountz and J. R. Smith (J. Clin. Investigation 17: 147, 1938) have reported large increases in coronary flow in perfused, revived human hearts after administration of digitalis bodies.

There were no significant changes in blood pressure following intravenous injections of subnauseating doses of the digilanids.

It is concluded that in subnauseating doses the three digilanids, A, B, and C, have no effect on the mean coronary blood flow in the trained intact dog.

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THE ACTION OF DIGITALIS ON THE ISOLATED HEART*

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INTRODUCTION

CLINICALLY, there are two opposing schools of thought concerning the action of digitalis on the heart. The English school, led by Mackenzie[1] and later by Lewis,[2] attributes the efficacy of the drug chiefly to its depression of auriculoventricular conduction. They advocate its use in heart failure with auricular fibrillation, but find it only occasionally of value in heart failure with sinus rhythm. The other school, led by Christian[3] in this country and Wenckebach[4] in Austria, attributes the action of the drug chiefly to its effect on the tone and contractile power of the heart muscle and advocates its use in all cases of congestive heart failure.

It is definitely established that digitalis depresses the conduction system of the heart and produces ectopic rhythms. It does so not only directly[5] but also by its action on proprioceptive vascular reflexes.[6] It has also been demonstrated that digitalis exerts an action on cardiac size and contractile power, although the exact nature of this effect has not been made clear (cf. Weese,[5] Cushny[7] for literature). It is not established whether this action of the drug is entirely an indirect one consequent to extracardiac changes in the circulation or in part a direct effect on the heart muscle.

There is ample evidence that digitalis produces changes in the peripheral circulation. For example, it has long been known that digitalis produces a vasoconstriction both of systemic[8] and pulmonary[9] arteries. In systemic vessels this has been shown to be, in part at least, a reflex effect.[6] Digitalis also has a vasoconstrictor action on veins.[10] In addition, it has been demonstrated[11, 12] that digitalis diminishes the venous return to the heart by contracting the blood vessels of the liver. The diuresis which the drug induces, although acknowledged to be secondary to circulatory changes,[13, 14] nevertheless itself alters the circulatory equilibrium[15] and so exerts an indirect effect on the heart. An additional factor is the decrease in blood volume which Wollheim[16] and others[17, 18] have found associated with the effect of digitalis.‡

Whether or not there is a direct action of digitalis on cardiac size and contractility, in addition to these indirect effects, cannot be ascertained

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‡Whether these complex effects of digitalis are in any way related to the action of the drug in decreasing tissue oxidation[19] remains to be determined.

by clinical observations or by experiments on the entire animal. This question can be settled only by observations on heart preparations in which the peripheral changes can be eliminated, or controlled and evaluated. A number of such preparations have been employed for this purpose, the most common being the heart-lung preparation. With this method Bijlsma and Roessingh[20] found a decrease in heart size with digitalis, and Cohn and Steele[21] an increase in cardiac output when the heart was in failure. An increase in mechanical efficiency of the heart due partly to a decrease in oxygen consumption and partly to an increase in work was observed by Gremels[22] in the heart-lung spirometer system. These observations on the heart-lung preparation were confirmed by other workers (Rühl and Wiehler,[23] Peters and Visscher[24] and Gollwitzer-Meier and Kruger[25]), and the phenomena were attributed by all these authors to a direct action of digitalis on the contractile power of the myocardium.

We have shown in a previous report[26] that the heart-lung preparation and the heart-lung spirometer preparation are subject to several sources of error. The most important are (1) that alterations in the pulmonary circuit due to vasomotor changes and pulmonary edema might lead to alterations in the relative diastolic size of the right and left ventricles which would not be apparent to the investigator, (2) that alterations in the partition of flow between the coronary sinus and other drainage channels[27, 28] would give variable false values for total coronary flow when measured with the Morawitz cannula, and hence for oxygen consumption, (3) that variation in the work of the right heart is not measured directly but is erroneously assumed to be a fixed proportion of the work of the left heart, and (4) that with the spirometer method varying degrees of pulmonary edema and variations in the metabolism of the lung introduce indeterminable errors in the calculation of the oxygen consumption of the heart.

It is apparent, then, that the question whether there is a direct action of digitalis on the contractile power of the heart can best be answered by studying its effect on the isolated heart. In such experiments the heart rate must either be kept constant, or the effect of changes in rate on metabolism, work, and heart size be evaluated before attributing them to digitalis. Some of the confusion in the earlier work can be ascribed to lack of appreciation of this fact. Moreover, the isolated heart preparation should simulate conditions in the animal as much as possible. The use of a modified Langendorf preparation or strips of cardiac muscle for this purpose[29-32] is too artificial to be satisfactory. In one experiment Rühl[23] used an isolated single heart circuit to study the effect of digitalis. The value of this method was lessened by two sources of error, namely (1) a Morawitz cannula was used to collect coronary sinus blood, and the coronary flow altered unphysiologically by the fact that this cannula was connected with atmospheric instead of auricular pressure,

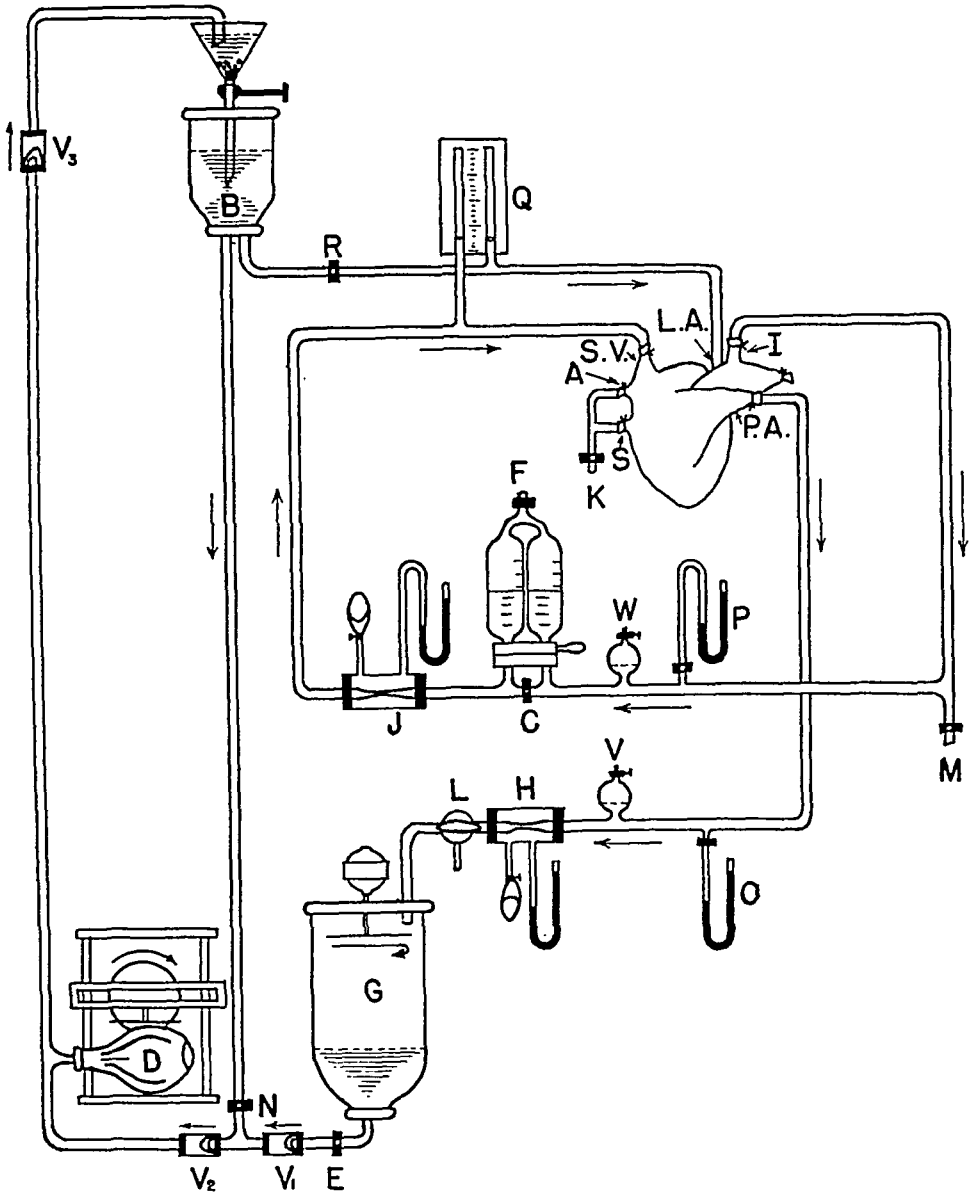

Fig. 1.—Diagram of the single isolated heart circuit. *PA*, cannulated left pulmonary artery; *I*, cannulated innominate artery; *LA*, cannula into left auricle; *SV*, cannulated superior vena cava; *A*, cannulated azygos vein; *S*, cannula in coronary sinus via inferior vena cava; *M* and *K*, sampling tubes; *P* and *O*, mercury manometers for aortic and pulmonary arterial pressures, respectively; *J* and *H*, aortic and pulmonary resistances, respectively; *W* and *V*, pressure bottles acting as elastic air cushions to smooth out aortic and pulmonary flows, respectively; *L*, three-way stop cock for measuring pulmonary flow; *F*, modified Ludwig stromuhr for measuring aortic flow (pinch-clamp, *C*, is removed except when aortic flow is being measured); *Q*, water manometers for right and left venous pressures; *G*, aerator enclosed in a thermostatically regulated cabinet; *B*, reservoir enclosed in a thermostatically regulated cabinet. The inflow from the funnel, at the bottom of which are glass beads acting as a foam-trap, is regulated by means of a screw-clamp in such a way as to keep the level of the blood in the reservoir constant. (This arrangement was suggested by Mr. H. Heintz.) A thermometer records the temperature of the reservoir blood. *D*, pump keeping the reservoir blood circulating and well mixed. *N* and *E*, pinch-clamps alternately applied as necessary in order to drain blood from *G*; *R*, screw-clamp regulating inflow; ↓ direction of blood flow. (Taken from Katz and Mendlowitz, J. Physiol. 92: 2P, 1938.)

and (2) the variable Thebesian flow into the right heart in the course of the experiment introduced variations of inflow into the circuit and uncontrolled variations in the oxygen content of the blood flowing into the coronary arteries. In the present study we used the isolated heart circuit which we have described previously.[26] This method eliminates most of the difficulties of other heart preparations and permits one to measure, with minimal error, the work, oxygen consumption and efficiency of the isolated heart beating under controlled conditions.

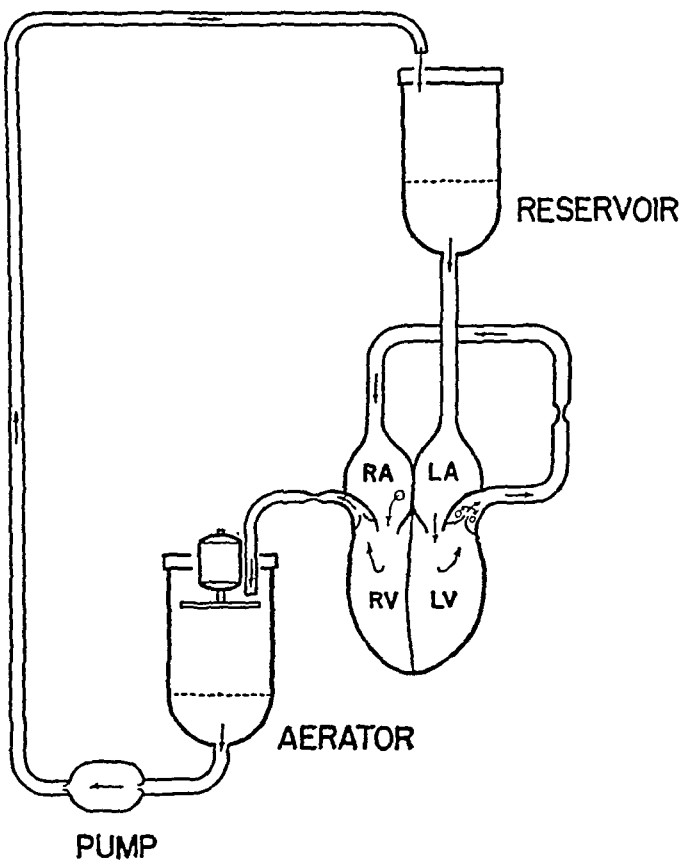

Fig. 2.—Diagram of course of blood circulation in the isolated heart circuit used in these experiments. (Taken from Katz and Mendlowitz, Am. J. Physiol. 122: 262, 1938.

METHOD

The method of establishing the isolated heart circuit as well as the means by which all of the variables are measured and calculated have been described in detail in a previous communication.[26] In brief, the classical heart-lung preparation is converted into a double, isolated heart circuit which in turn is converted into the single circuit. In this circuit, the defibrinated and heparinized blood enters the heart via the left auricle, from a reservoir, under constant pressure. It is pumped by the left ventricle through an artificial resistance into the right auricle, and then by the right ventricle through an artificial resistance into an aerator from which an artificial pump forces it back into the original reservoir. A diagram of the single isolated heart circuit is shown in Fig. 1, and the course of the blood circulation in Fig. 2.

Eight experiments were performed. In seven of these, after the circuit was established and the desired levels for blood flow and pressures obtained, no further readjustments were made except in the pulmonary and aortic resistances, which were varied in order to keep the aortic and pulmonary arterial pressures as constant as possible. In the remaining experiment, the work of the heart was kept constant by adjusting the inflow pressure and the arterial resistances so that outflow and pulmonary and systemic arterial pressures were constant. The effect of the drug was studied on the spontaneously failing heart in 7 experiments, and on a "physiologic" heart, i.e., before failure was manifest, in one instance.

The drugs used were digifoline, digoxin, and ouabain.* The digitalis glucosides were introduced into the inflow reservoir in divided doses of usually ½ to 1 cat unit. The initial range of concentration was computed to be equivalent to from 1:70,000,000 to 1:35,000,000 ouabain solution. The number of doses used ranged in any one experiment from one cat unit in a single dose to a maximum of seven cat units divided into five doses given over a period of as long as two hours. In the divided dosage, the glucoside was given at intervals varying from 5 to 40 minutes. Measurements were made before digitalis was given and at 1- to 2-minute intervals

TABLE I

EFFECT OF DIGITALIS ON ENERGETICS OF SPONTANEOUSLY FAILING ISOLATED HEART WHEN ITS WORK IS KEPT CONSTANT

TIME (MIN.)	HEART RATE (BEATS/MIN.)	LEFT VENOUS PRESSURE (CM. H_2O)	RIGHT VENOUS PRESSURE (CM. H_2O)	CORONARY FLOW (C.C./MIN.)	O_2 CONSUMPTION (C.C./MIN.)	WORK (KG./HR.)	MECHANICAL EFFICIENCY %
0	152	2.4	3.5	234	7.9	37.6	3.7
6½	144	3.2	4.5	246	7.2	36.9	4.0
15	148	4.4	6.0	259	8.1	38.2	3.7
50	152*	9.7	12.5	255	9.2	34.6	3.1
64½	132	17.5	18.5	226	7.0	34.1	3.8
79	116	32.5	24.5	217	7.1	37.2	4.1

*At this time extrasystoles were more frequent and runs of paroxysmal tachycardia were present.

1 cat unit of digifoline (Ciba) was added six times to the blood reservoir, viz: 7, 16½, 30, 40, 52 and 66 minutes after sample 1 (zero time).

TABLE II

EFFECT OF SPONTANEOUS HEART FAILURE ON ENERGETICS OF ISOLATED HEART WHEN ITS WORK IS KEPT CONSTANT

TIME (MIN.)	HEART RATE (BEATS/MIN.)	LEFT VENOUS PRESSURE (CM. H_2O)	RIGHT VENOUS PRESSURE (CM. H_2O)	CORONARY FLOW (C.C./MIN.)	O_2 CONSUMPTION (C.C./MIN.)	WORK (KG./HR.)	MECHANICAL EFFICIENCY %
0	105	9.5	2.5	125	6.5	18.2	2.2
13	104	11.0	2.7	128	6.1	19.8	2.6
38	108	12.2	3.2	148	6.5	19.2	2.3
58	108	14.4	3.9	155	7.0	19.0	2.1
73	108	18.7	5.0	146	6.5	19.0	2.3
88	108	25.5	6.8	122	6.5	18.7	2.3

*Obtained through the courtesy of the Ciba Company, the Burroughs Wellcome Company, and the Abbott Laboratories, respectively.

thereafter until toxic symptoms were manifest. Blood samples were taken at 5- to 20-minute intervals during the course of the experiment.

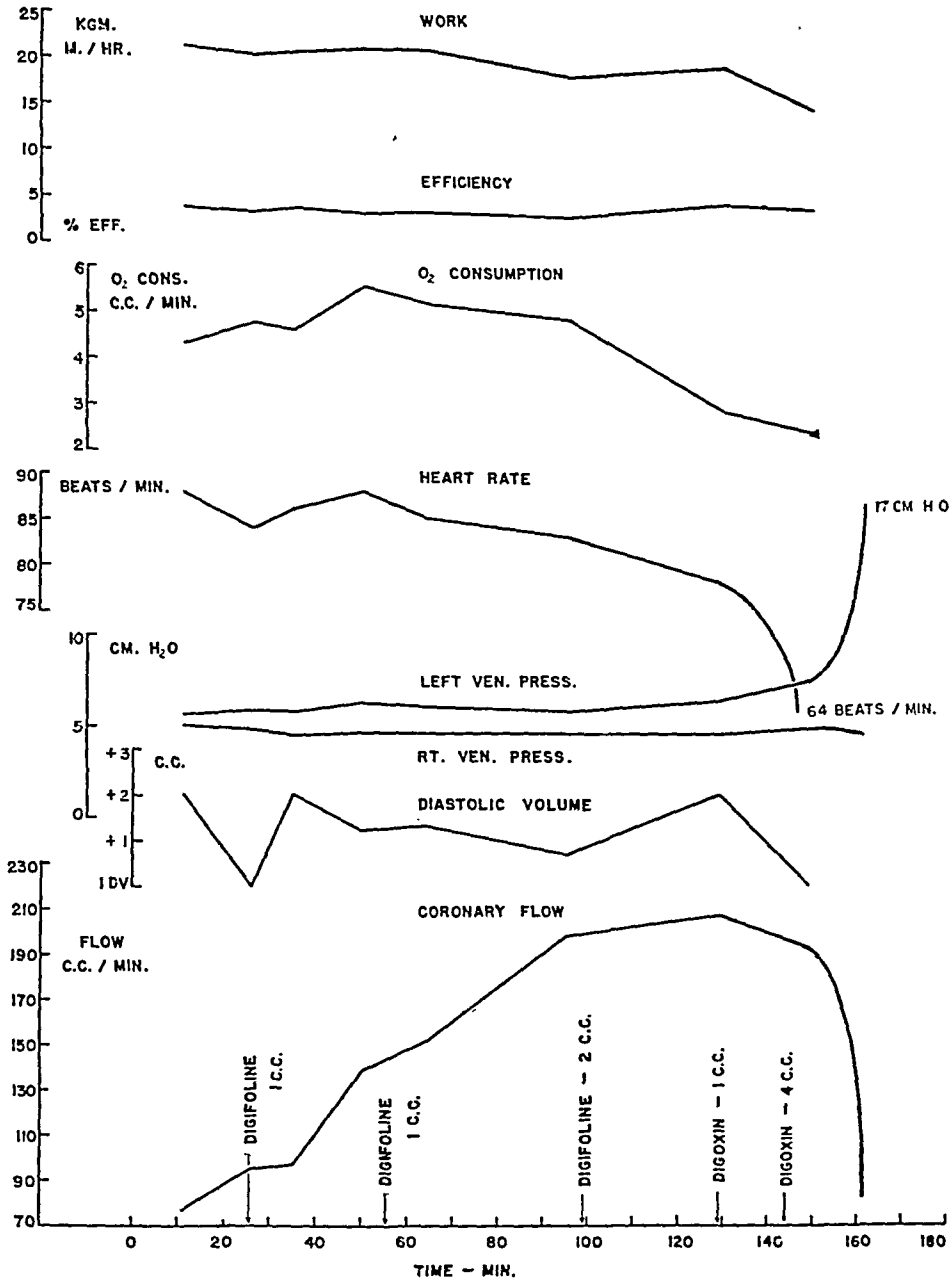

Fig. 3.—Pertinent data of an experiment in which the inflow pressure head and the aortic and pulmonary arterial pressures were artificially kept constant, showing the effect of divided doses of digitalis. Digitalis, in this instance, was begun before spontaneous heart failure developed. The digitalis was put in the inflow reservoir. The concentration of digitalis in this experiment and that shown in Fig. 3 can be computed in terms of ouabain equivalents. (1 c.c. digoxin = 0.1 mg. ouabain = 1 cat unit. The quantity of blood in the perfusion system is approximately 3,500 c.c.)

RESULTS

The results of the experiment before heart failure was manifest, and of a typical one after failure had developed, are shown in Figs. 3 and 4, respectively. In the preparation which showed no heart failure when digitalis was started (Fig. 3), there were no significant changes in heart

size, flow, work, oxygen consumption or mechanical efficiency until the toxic effects on conduction began to appear. In this experiment coronary dilatation began before the administration of digitalis and progressed during the course of the experiment until heart failure set in. In the failing heart (Fig. 4), the work decreased, the oxygen consumption also

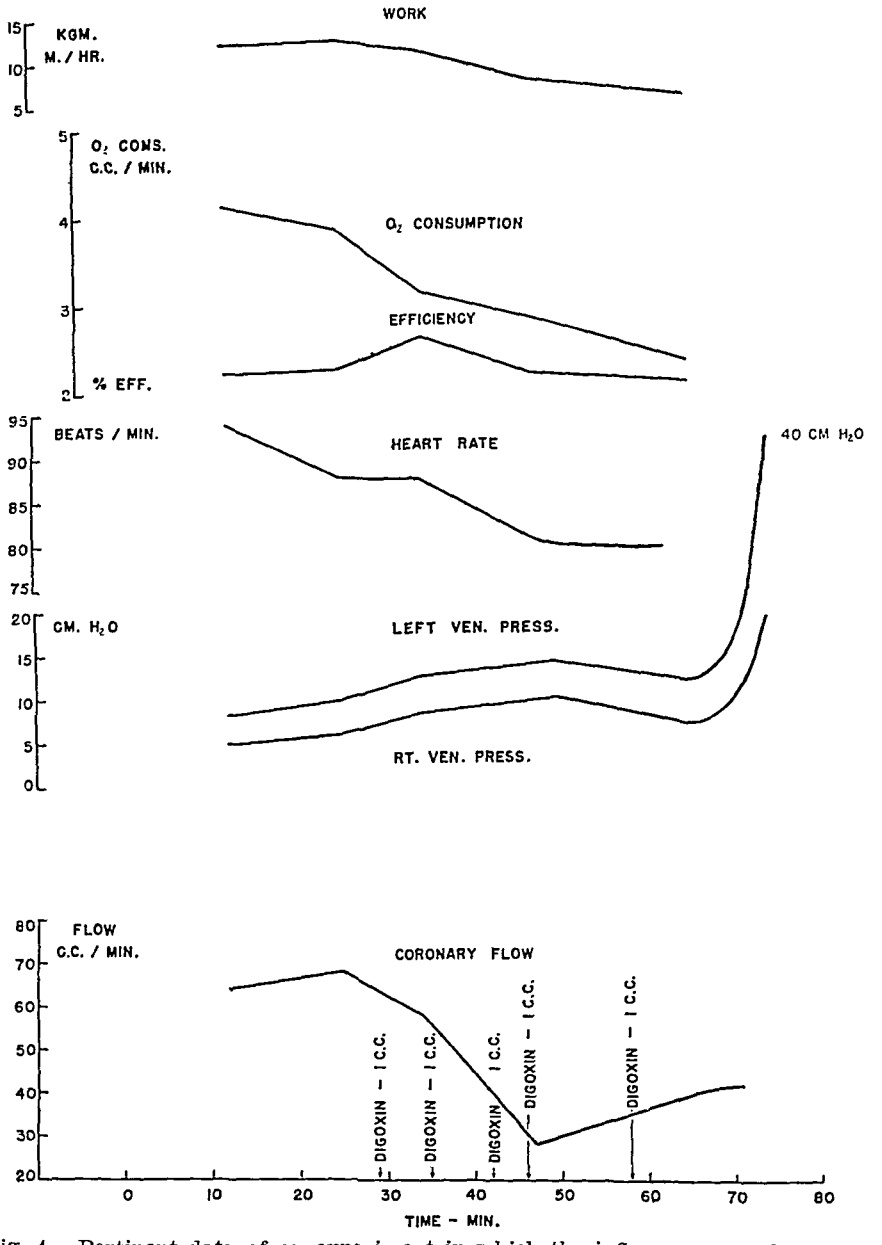

Fig. 4.—Pertinent data of an experiment in which the inflow pressure head and the aortic and pulmonary arterial pressures were artificially kept constant, showing the effect of divided doses of digitalis. Digitalis was administered as spontaneous heart failure appeared.

decreased, and the mechanical efficiency remained relatively unchanged. These changes are similar in all respects to those found in spontaneous heart failure without digitalis[26] (cf. Fig. 5). When the work of the heart was kept constant (Table I), digitalis produced no change in oxygen

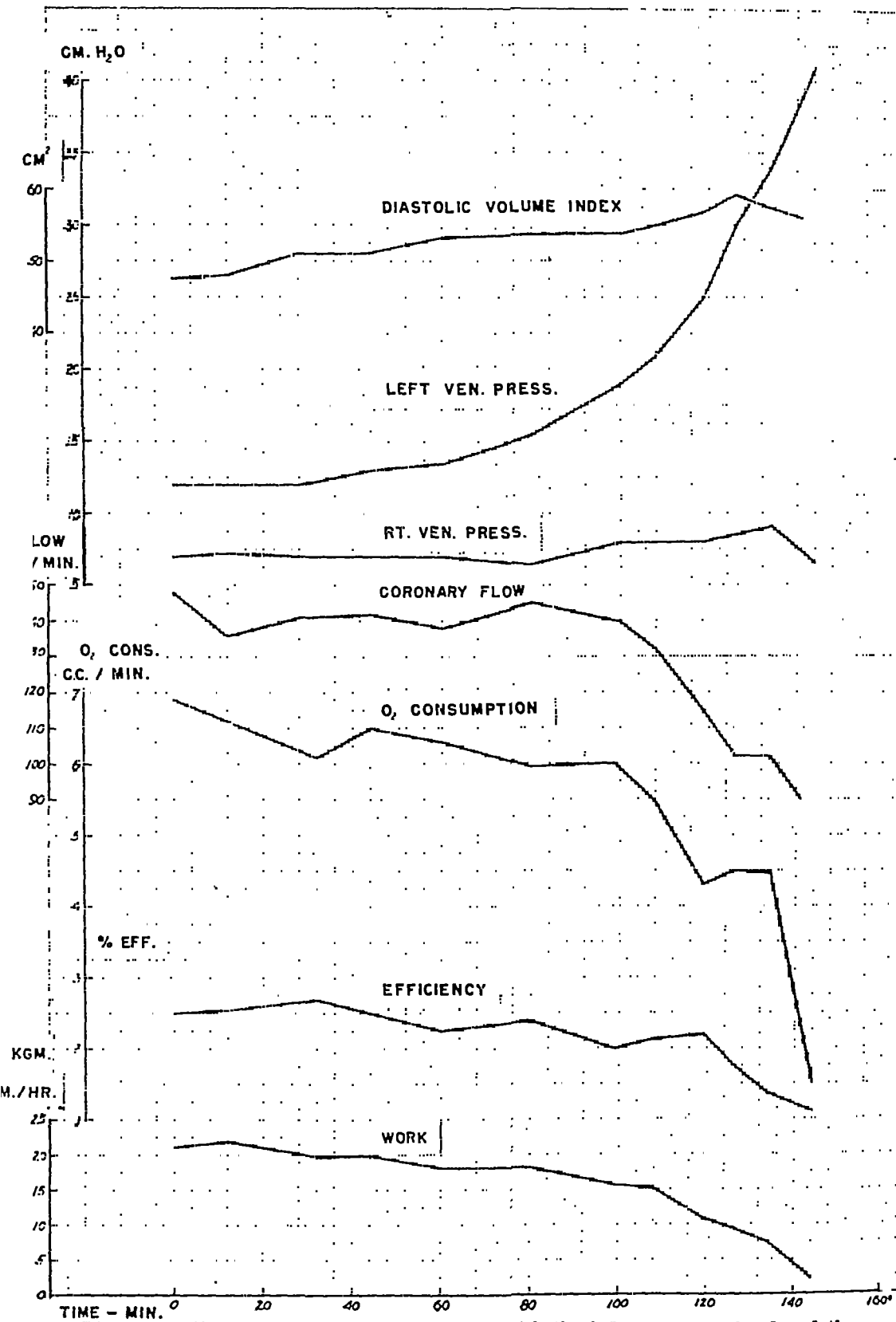

Fig. 5.—Pertinent data of an experiment in which the inflow pressure head and the aortic and pulmonary arterial pressures were artificially kept constant, showing the effect of spontaneous heart failure. (Taken from Katz and Mendlowitz, Am. J. Physiol. 122: 262, 1938.) Note the similarity between this experiment without digitalis and that illustrated in Fig. 4, in which digitalis was administered.

consumption or efficiency. As in the control experiment without digitalis (Table II), they both remained constant despite a progressive increase in heart size and venous pressure. The decrease in the ratios $\frac{\text{work}}{\text{diastolic size}}$ and $\frac{\text{oxygen consumption}}{\text{diastolic size}}$ were not discernably greater in heart failure with digitalis than without it. The ratio $\frac{\text{work}}{\text{oxygen consumption}}$ i.e., the mechanical efficiency, as in heart failure without digitalis, remained unchanged in failure with digitalis. The only effects of the drug consistently observed were therefore the ectopic rhythms and effects on conduction. These appeared in every experiment in the form of extrasystoles (sometimes ventricular tachycardia), A-V heart block, and terminal ventricular fibrillation.

It is apparent that, in our preparation, digitalis did not have any significant effect on the contractility of heart muscle, whether the heart was in failure or not. Its only direct effect appeared to be on the conduction system and ectopic pacemakers of the heart.

Although no sweeping conclusion can be drawn concerning the action of digitalis in human heart failure, the results which we have obtained raise a definite objection to the acceptance of the idea that there is a direct action of the drug on the contractile power and energetics of the heart. This objection seems particularly pertinent since the action of digitalis in man, i.e., its ability to decrease the load on the heart, can be satisfactorily explained by its effect on the peripheral circulation.

SUMMARY

A method is described for studying the direct action of digitalis on the isolated dog's heart. The results indicate that digitalis has no direct effect on the contractile power or mechanical efficiency of the heart muscle, either in the "physiologic" or the failing heart. The only direct cardiac effects found were changes in conduction and the development of ectopic rhythms. The effects of digitalis in human heart failure are discussed in the light of these results.

We are indebted to the other members of the department for their assistance in these experiments.

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GRADUAL OCCLUSION OF A CORONARY ARTERY

An Experimental Study*

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During the course of experiments concerned with the augmentation of the blood supply to the heart, it became apparent that a definitive investigation of gradual coronary occlusion was desirable. The reasons for this are as follows:

1. In contrast to the effects of acute coronary occlusion, which have been described and reviewed in repetitive detail ever since Cohnheim, there are few experimental data pertaining directly to gradual closure.

2. An article on the benefits of cardiopexy appeared in which obturation of the coronary vessels was obtained by repeated pinching of metal clips.[9] Since the validity of this work is entirely dependent on the establishment of controls, which were not mentioned, we thought that our results might be particularly relevant.

3. Something might be learned about the mechanism of the collateral coronary circulation. In this connection it is interesting to note that in 1903 Galli commented on the controversy between the adherents of Cohnheim, who considered the coronary vessels to be end arteries, and the followers of Vieussens, Thebesius, and Sappey, who believed that the blood vessels of the heart formed an anastomosing network.[1]

4. The opportunity to attempt to simulate degenerative disease in the experimental animal was a particularly inviting one.

5. The elaboration of a successful technic for the gradual, controlled closure of a major intrathoracic vessel would make possible, and so invite, further experimentation.

It is known that interruption of the coronary blood flow, if gradual, is not incompatible with life, as the case reports of Leary and Wearn,[2] Graetzer,[3] Bellet and others[4] attest. LeCount,[5] in a discussion of the pathology of angina pectoris, remarked that coronary atherosclerosis with gradual constriction resulting in myocardial fibrosis was very common and, if sufficiently slow in development, symptom-free. A statistical restatement of this view was made by Brown,[6] who found definite arteriosclerosis in 98 of 110 unselected hearts which showed a typical pattern ("ischemic necrosis") of myocardial fibrosis.

In 1935 Robertson[7] occluded the major coronary vessels in dogs by serial ligation over a period of months. The multiple procedures necessary in this method resulted in the formation of dense vascular adhesions which he considered of greater importance in the nourishment of the myocardium than the Thebesian system or the vessels of the pericardial

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mantle. There were three factors involved in the conduct of this experiment which seem to vitiate its application to any clinical problem. First, ligation of the coronary sinus, which he performed to prevent backflow, does, of itself, definitely influence coronary blood flow.[8] Second, the operative production of vascular adhesions represents a complication which does not ordinarily obtain in the human heart. Third, a series of consecutive ligations, however well graded, would seem to resemble repeated acute occlusions rather than gradual narrowing. Beck and Tichy have demonstrated the effects of cardiopexy in the dog.[9] Coronary occlusion was effected by the repeated pinching of metal clips placed near the origins of the vessels. There was no mention of control animals in which obturation was produced without the formation of adhesions. In an article just published,[10] Beck states that he is remedying this defect. He is apparently employing a method which is undoubtedly very similar to ours, so that a direct comparison of observations will be possible. Until this important point is clarified, the benefits of cardiopexy must be considered as presumptive rather than proved.

In a discussion of the dynamic factors concerned in the development of collaterals during slow coronary occlusion, Wiggers[11] has expressed a rather pessimistic opinion of both the caliber and functional ability of potential communications. He does, however, grant that the slow establishment of differential pressure gradients might distend, and so render effective, normally useless vessels.

Our experiments will be presented by separately considering the technic, the conduct (typical protocol) of the work, and the results.

TECHNIC

A two-piece screw clamp, resembling the one used by Goldblatt, but simpler, is employed in the manner illustrated in Fig. 1. In the dog, ample exposure is obtained through an incision in the left fifth intercostal space (Spangaro). The left lung is deflated and packed off. A short incision, parallel to, and just anterior to, the phrenic nerve, is made in the pericardium over the site of origin of the anterior descending branch of the left coronary artery. At a point 2 to 3 cm. from its origin, two short parallel nicks are made in the epicardium on either side of the artery and its venae comites. A fine curved hemostat is then used to establish a plane of cleavage between the cuts and beneath the vessels. The clamp piece is then placed through this dissected opening so that the artery, its venae comites and the overlying strip of epicardium are all embraced in the jaw of the clamp piece. The threaded clamp arm is then introduced and screwed down in the clamp piece so that, although the vessels are not in the least squeezed, they cannot escape from the grasp of the instrument. The pericardial wound is closed with interrupted silk sutures so as to avoid any tension on the clamp. The chest wall is sutured in layers in such fashion as to produce an airtight closure without causing any deviation of the clamp arm. The latter is bent to a right angle about one inch above the surface of the skin. It is then clipped off at a length suitable to easy turning. A protective wire basket is strapped over the protruding clamp, which oscillates freely with the heartbeat.

The venae comites and overlying epicardial strip are included with the artery because they serve to cushion it and counteract the unavoidable, though slight, drag

of the clamp. We know from previous experience that the coincidental venous occlusion at this point is of no apparent significance.

The greatest care is taken to avoid any trauma to the visceral pericardium except that necessary at the point of application of the instrument. In each dog, a note is made of the number of turns necessary to close the clamp completely.

TYPICAL PROTOCOL

Dog 348, a large (25 lb.) mongrel of the beagle type, was totally anesthetized by means of an intravenous injection of nembutal, and an electrocardiogram was made. The procedure described above was then performed, care being taken that the artery

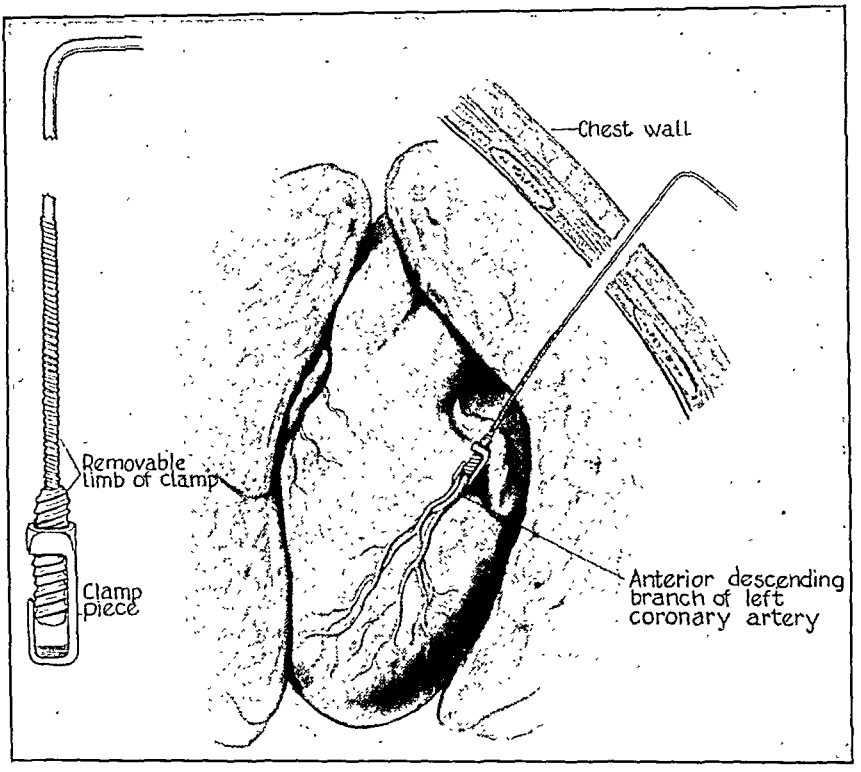


Fig. 1.—Method of applying the coronary clamp.

was neither compressed nor kinked. The wound was dressed on alternate days, and electrocardiograms were secured at intervals. The clamp was tightened as follows:

½ turn on the 7th day; ½ turn on the 10th day; ½ turn on the 16th day;
½ turn on the 25th day; ½ turn on the 30th day; ½ turn on the 32nd day;
½ turn on the 35th day; ½ turn on the 39th day; ½ turn on the 42nd day;

On the forty-seventh day, the animal was killed, and the thoracic viscera were carefully examined. As soon as the gross appearances were noted, the heart was injected according to a standardized technic. Sections for microscopic examination were cut, and roentgenograms of the injected heart were taken.

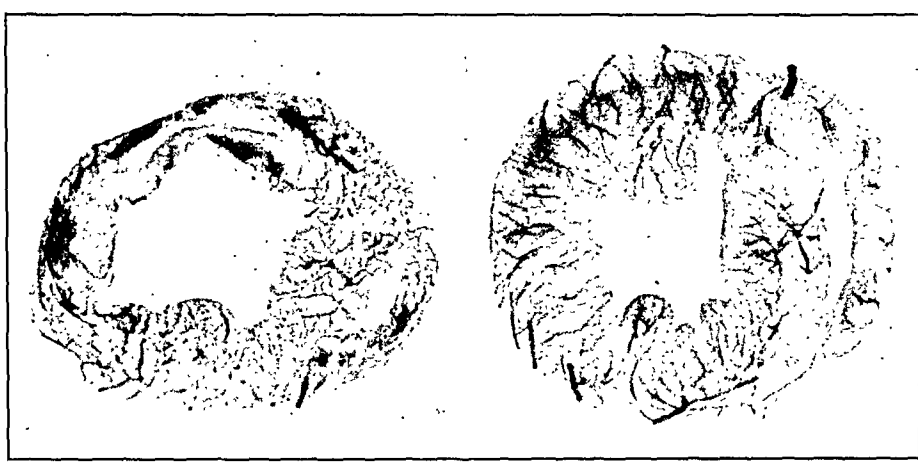
RESULTS

The animals used may, for clarity's sake, be divided into five groups. The first group comprises fourteen dogs in which the anterior descending branch of the left coronary artery was gradually occluded over a period

averaging five weeks in duration. Since these animals serve as the nucleus of the experiment, they will be presented first.

At necropsy, the artery was found to be completely shut off in all fourteen dogs, and in half of them the clamp had sloughed through the necrotic vessel and was found in the chest wall. In each, there was a plaque of fibrous adhesions, 1.5 cm., or less, in diameter, at the operative site, which marked the cardiac end of the granulation tissue-lined tract extending about the clamp to the skin. In only one (No. 309) of these dogs, surprisingly enough, did a pleural fistula develop, and this healed by the end of the second week.

In none of these fourteen dogs was there any evidence of an adhesion in the pericardial cavity over the anterior surface, the apex or any portion of the heart supplied by the occluded vessel, except that mentioned above.



A. *B.*

Fig. 2.—*A*, roentgenogram of injected heart taken one week after sudden occlusion of anterior descending branch of left coronary artery.

B, roentgenogram of injected heart taken after the anterior descending branch of the left coronary artery had been progressively narrowed at one point until, at the end of five weeks, occlusion became complete.

In ten of these fourteen dogs there was no gross evidence of an infarct. Of the other four, there were two with recognizable but comparatively small areas of tissue damage located in the anterior wall of the left ventricle just above the apex. The remaining two animals showed fairly large infarcts with aneurysmal dilatation of the left ventricular wall.

Microscopic examination showed no evidence of tissue abnormality in four of these fourteen dog hearts. In six the histologic appearance was distinctly reminiscent of human coronary sclerosis. The pathologic pattern was one of graded degrees of damage ranging from areas in which there was merely a fading of striations in the muscle to those in which the field was composed of scar tissue. The intermediate changes were represented by scattered foci of cells containing pigment, which lay in loose connective tissue and frequently adjoined normal muscle fibers in one quadrant of the field, and denser scar tissue in another. In short,

the process was one of atrophy with muscle fibers grading into fibrotic areas of replacement, and not one of acute necrosis as seen in the control animals. Sections in the remaining four dogs revealed analogous but more marked changes. The lesion was qualitatively similar, but the myocardial damage was evidently greater, though in no wise comparable to that of the control animals.

All fourteen hearts were injected while still fresh, according to the method of Gross. One injection was incomplete due to a technical error. Ten hearts showed a normal vasculature. In the remaining three, a defect was discovered. In some of the dogs there seemed to be a septal defect which was thought to be due to injury of the septal branch artery which comes off at the site of application of the clamp. However, histologic study revealed no tissue damage in this area which might indicate that the trouble was related to the injection. Since the value of injection studies has been questioned because of an asserted lack of correlation between the anatomical disposition of a vascular field and its functional status, we are content to offer this portion of our data as merely presumptive evidence for comparison with our control findings.

Electrocardiograms were obtained in each of these fourteen dogs. They all showed, at one time or other, positive or strongly suggestive signs of coronary occlusion. It is interesting to note that the mere presence of the clamp was associated with changes in three animals, and that in five others the tracings were normal. A detailed analysis of the electrocardiographic data would be of questionable value at this time.

The second, or control group, is composed of twenty-five dogs surviving acute occlusion of the anterior descending branch of the left coronary artery at that point at which the clamp was placed in the animals of the previous group. The vessel was divided between ligatures. At necropsy, performed one week after this procedure, a large infarct occupying the anterior wall of the heart was found in every instance but one. This dog showed only a small infarct just above the apex. Microscopically, there was massive, homogeneous necrosis of the involved area, i.e., acute myocardial infarction. An injection defect was found in 15 of the 25 dogs. The electrocardiographic changes were characteristic of acute coronary occlusion in the dog.

The third group is composed of the seventeen animals which died. Two fatalities were deferred; one was due to snuffles, and the other, to fistula formation with pyopneumothorax. The other fifteen deaths were postoperative; of these, five were due to pneumonia, two to shock, one to secondary hemorrhage, and two to heat exhaustion. It is significant that in these animals the coronary artery was patent despite the fact that the untightened clamp had been present for a considerable period of time. This demonstrates that the unavoidable tug and stress at this point due to the cardiac and respiratory movements did not result in traumatic thrombosis, and confirms our belief that constriction of the vessel was actually controlled with the clamp.

The fourth group comprises two dogs in which acute occlusion occurred accidentally. In one of our first experiments we constricted the artery too rapidly, with the result that the dog died of ventricular fibrillation three minutes afterward. In the other, also one of the first animals, the clamp was turned too frequently, and the dog died after thirteen days. A large infarct resembling those seen in the control group was found.

In the fifth group, which includes six dogs, autopsy disclosed that either the clamp had slipped or only a minor branch had been occluded.

SUMMARY AND CONCLUSIONS

Of fourteen normal dogs in which the anterior descending branch of the left coronary artery was gradually occluded without the formation of adhesions, no evidence of tissue damage was found in four; scattered changes in the myocardium resembling those seen in human coronary sclerosis with stenosis occurred in six; and in the remaining four more extensive myocardial lesions were present. Confirmatory injection studies and electrocardiographic observations were made.

The results indicate that when a major coronary artery in the dog's heart is progressively narrowed at one point until, at the end of five weeks, occlusion becomes complete, the collateral circulation which develops is sufficient to prevent a large part of the myocardial damage which occurs when the same artery is suddenly occluded at the same point.

Evaluation of the benefits of any experimental or clinical procedure designed to increase the coronary circulation during a period of gradual closure of a major vessel must be deferred until a biometric estimate of the time and other factors can be made.

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ELECTROCARDIOGRAMS IN WHICH THE MAIN INITIAL VENTRICULAR DEFLECTIONS ARE DIRECTED DOWNWARD IN THE STANDARD LEADS*

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FEW examples of electrocardiograms in which the main initial deflections are directed downward in all three leads are found in the literature. Willius[1] published serial electrocardiograms in one case in which this change occurred shortly after coronary occlusion, but he did not comment on it specifically. Bainton and Burstein[2] obtained similar tracings in a case of recent coronary occlusion. Another such electrocardiogram was regarded by Wilson, Johnston, and Barker[3] as an example of an unusual form of right bundle branch block (their Fig. 1, p. 473); the patient was a negro, 37 years of age, who had had severe bronchial asthma for three years.

Downward deflection of the main ventricular complexes in the three standard leads is difficult to explain by Einthoven's triangulation method for determining the electrical axis of the heart. It has frequently been shown that this method has many limitations. Pardee[4] has pointed out that the usual statements regarding axis deviation apply only to records in which the QRS group is normal except for the axis deviation. Thus, in cases in which the QRS group is abnormal (notched, slurred, and prolonged) in more than one lead, the preponderant hypertrophy of one or the other ventricle may not determine the axis deviation. In such a case the whole spread of contraction may be abnormal, and this is likely to completely overbalance the effect of abnormal ratio of ventricular weights. Myocardial disease, by injuring the conducting tissues of the heart, may interfere with the normal spread of contraction.[5] That abnormal distribution of bundle arborizations may invalidate the Einthoven method of determining ventricular preponderance has also been suggested.[6, 7]

A frequent criticism of the Einthoven method is that it does not take sufficiently into account the important role played by the conducting tissues about the heart in determining the form of the electrocardiogram. Pericardial effusion or massive edema of the extremities may decrease the amplitude of electrocardiographic deflections,[8] and in pulmonary emphysema the lung tissue which overlaps the heart may decrease the voltage by short-circuiting the heart's current.[9] Robinow[10] recently re-

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ported a proved case of dextrocardia in which the electrocardiogram showed left axis deviation, and collected four similar cases from the literature. In such instances it is difficult to harmonize the electrocardiogram with Einthoven's concept. Katz[11] believes that these unexpected findings may be accounted for by changes in the relationship between the heart and the structures surrounding it. He stresses the influence of the electrical field about the heart upon the electrocardiogram and finds that electrocardiographic tracings register events in favored regions of the heart, rather than in all regions.

Since 1929, when the Morrisania City Hospital was established, electrocardiograms have been taken in 15,000 cases, in only nine of which were the main initial deflections directed downward in the standard leads. It is significant that recent coronary occlusion was known to be the etiologic factor in five of these cases (Nos. 1, 2, 5, 7, and 8) and was regarded as the most likely cause in three others (Nos. 4, 6, and 9). One patient (Case 3) probably had pericardial effusion. The incidence of pulmonary disease in this group was also interesting. Six of the nine patients (Cases 2, 3, 4, 5, 6, and 8) either gave a history of bronchiectasis or bronchial asthma, or presented objective evidence of bronchiectasis or other chronic pulmonary disease. Four patients (Cases 1, 2, 6, and 9) had pleural effusion at the time the electrocardiograms were made, and two (Cases 3 and 9) probably had pericardial effusion. One patient (Case 7) with typical clinical and electrocardiographic signs of recent coronary occlusion showed downwardly directed initial deflections in the standard leads only after terminal bronchopneumonia developed.

In each case an attempt was made to determine as far as possible the conditions which seemed to influence the production of downward deflection of the initial ventricular complexes in the standard leads.

REPORT OF CASES

CASE 1.—A 52-year-old negro entered the hospital Nov. 11, 1935, in advanced congestive failure. During the six months preceding admission he had had several attacks of severe substernal pain radiating to the epigastrium. The blood Wassermann and Kahn reactions were weakly positive (1+). The blood pressure was 110/90. Roentgenograms revealed a greatly enlarged heart, moderate diffuse enlargement of the aorta, and right-sided pleural effusion. Electrocardiograms made during the first week in the hospital showed atypical bundle branch block and complete A-V heart block (Figs. 1*A*, 1*B*). Two weeks after admission the signs of failure had disappeared, and the electrocardiogram showed left bundle branch block with first-stage conduction block and 2:1 A-V heart block in Leads II and III (Fig. 1*C*). Digitalis brought about further improvement in the patient's condition, and within the next three weeks electrocardiograms revealed left bundle branch block with complete A-V block (Fig. 1*D*) which in ten days changed to partial A-V block (Fig. 1*E*). On Jan. 11, 1936, when the patient left the hospital, roentgenologic examination revealed no abnormality of the lungs; the blood pressure was 170/100, and 2:1 A-V heart block was present (Fig. 1*F*). Diagnoses: Syphilis; arteriosclerotic and syphilitic heart disease; cardiac enlargement, myocardial fibrosis, coronary thrombosis; A-V heart block varying in degree from 2:1 to complete The functional classification was IIb.

In this case the change from downward deflection of the ventricular complexes in the three leads to left bundle branch block coincided with the disappearance of the pleural effusion.

CASE 2.—A 59-year-old white man entered the hospital Sept. 17, 1934, complaining of severe precordial pain radiating to the left shoulder. He had marked congestive

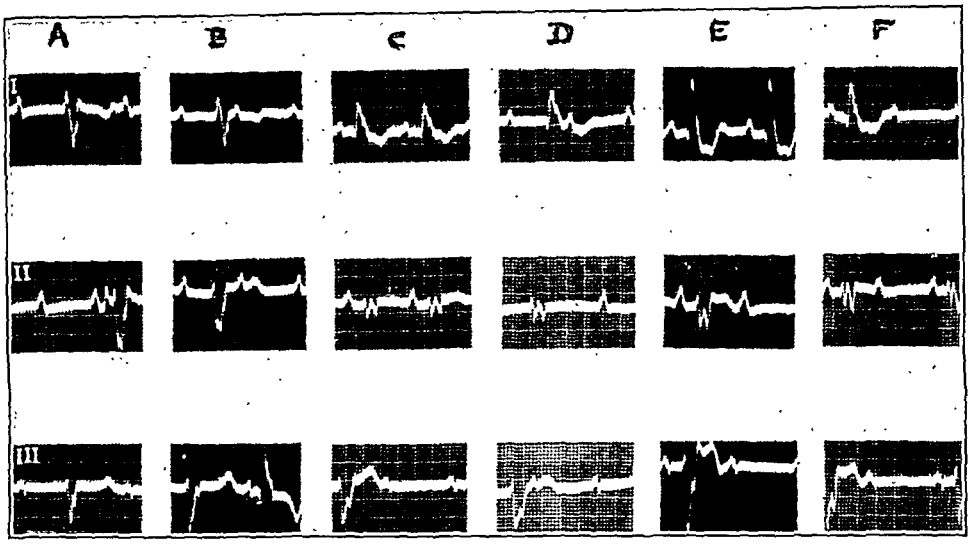

Fig. 1.

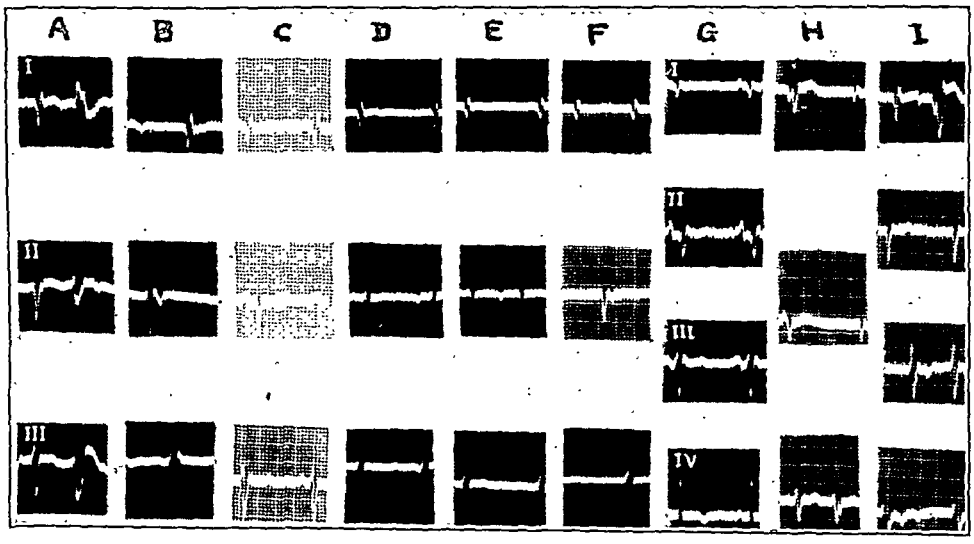

Fig. 2.

failure. His blood pressure was 140/74, and his blood Wassermann reaction was negative. An electrocardiogram on admission revealed complete heart block with coupled beats. There was a large Q-wave in Lead I. The initial deflections were directed downward in the standard leads (Fig. 2*A*). A week later the rhythm was of nodal origin (Fig. 2*B*). Roentgenologic examination showed that the heart was enlarged in all directions; the configuration suggested hypertension. There was thickening of the pleura over the base of the right lung, and generalized fibrosis of both lungs, most marked at the bases. One month after admission the patient had

a second coronary occlusion, which was followed by a large right-sided pleural effusion. He improved after thoracentesis, and sixteen days later left the hospital against advice. His blood pressure at this time was 100/74. The electrocardiogram showed regular sinus rhythm (Fig. 2*C*).

The patient returned to the hospital Dec. 12, 1934, with essentially the same complaints as before. Electrocardiograms made at this time showed that the downwardly directed initial deflections in the three leads were still present. The mechanism, however, had changed to auricular fibrillation (Fig. 2*D*, *E*, *F*). On Feb. 2, 1935, he was discharged greatly improved, but still with fibrillation. He next entered the hospital Sept. 6, 1937, following another coronary occlusion. The initial deflections were still directed downward, but the mechanism was normal. The Q-wave was absent from the precordial electrocardiogram (Fig. 2*G*) made by Wolferth's method.[12] Two weeks after admission he again experienced precordial distress, and thereafter had auricular fibrillation (Fig. 2*H*). One month later, with fibrillation still present (Fig. 2*I*) he left the hospital.

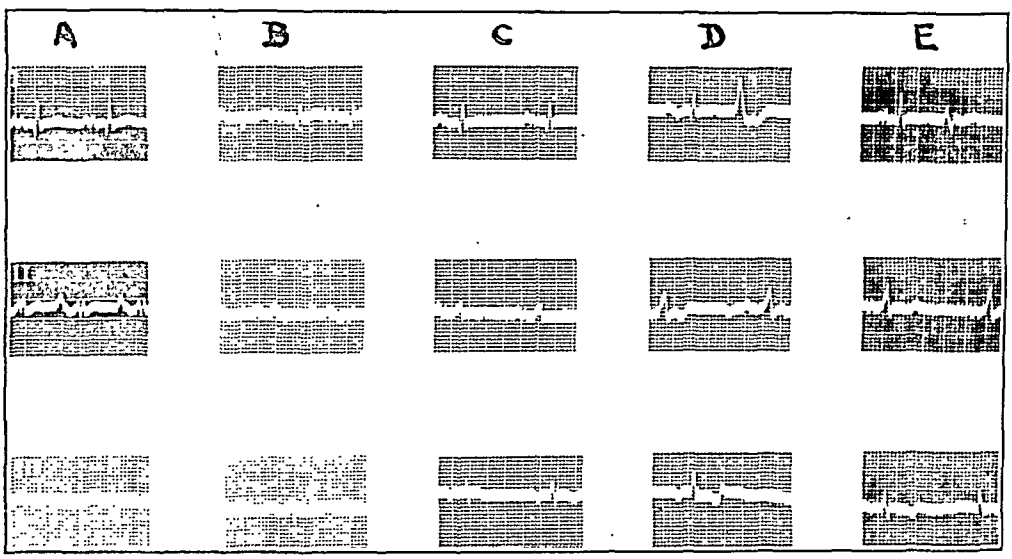

Fig. 3.

In this case the negativity of the initial deflections was known to be present for three and one-half years and did not seem to depend on extracardiac factors.

CASE 3.—A 49-year-old negro entered the hospital Oct. 11, 1935, with marked congestive failure. The history was that of progressive diminution of cardiac reserve for a year. He had suffered from bronchial asthma for about fifteen years, and from occasional "rheumatic" joint pains for about five years. The blood pressure was 100/70. The blood Wassermann reaction was negative. Diagnoses: Rheumatic heart disease; cardiac enlargement, mitral insufficiency and stenosis; regular sinus rhythm with premature contractions. The functional classification was III.

The electrocardiogram revealed left axis deviation; low voltage of the QRS complexes; notched, prolonged P-waves in all three leads; ventricular premature contractions; depressed T-waves in Leads I and II; slight inversion of T_3; and a first-stage conduction block with a P-R interval of 0.23 sec. (Fig. 3*A*). A few days later, when pericardial effusion developed, the main initial deflections became directed downward in the three leads (Fig. 3*B*). In tracings obtained after disappearance of the effusion the main deflections were upright in the limb leads (Fig. 3*C*, *D*, *E*). When the patient was discharged, Nov. 26, 1935, he was symptom-free.

It seems probable that the downward deflection of the ventricular complexes seen in one electrocardiogram (Fig. 3*B*) was due to pericardial effusion, for the complexes became upright again after the effusion disappeared.

CASE 4.—A 53-year-old white man entered the hospital June 20, 1934, because of a severe asthmatic attack. He had had bronchial asthma for ten years, and occasional anginal attacks on exertion for three years. His blood pressure was 110/74. An electrocardiogram revealed slurred and downwardly directed initial deflections in the limb leads (Fig. 4*A'*). After twelve days he was discharged as improved. Unknown to us, he re-entered the hospital Sept. 10, 1937, in status asthmaticus, from which he did not recover. No electrocardiograms were obtained and permission for autopsy was not granted.

The history of anginal attacks makes it likely that this patient had myocardial infarction in addition to his bronchial asthma.

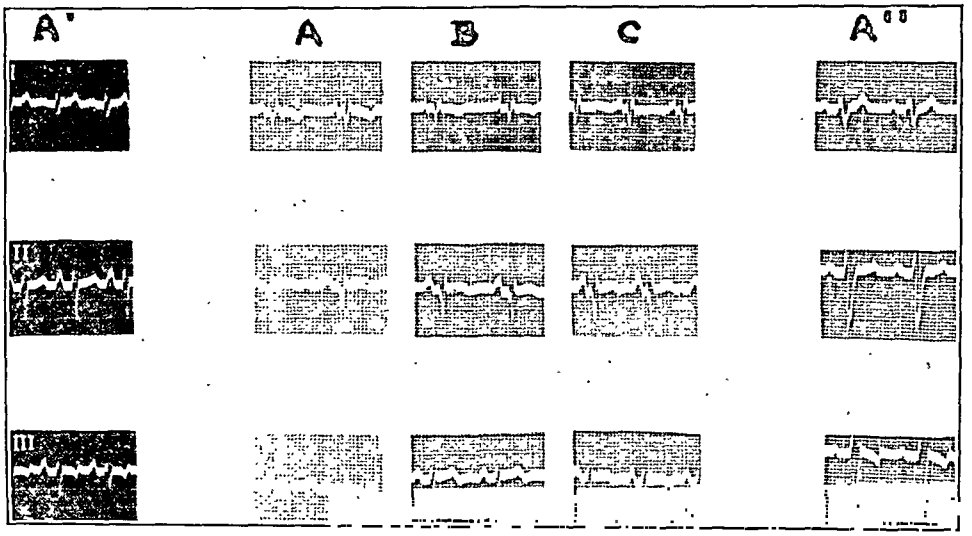

Fig. 4.

CASE 5.—In January, 1937, a 50-year-old white man was admitted to Mount Sinai Hospital because of coronary occlusion. At that time his electrocardiogram revealed evidence of acute infarction of the anterior wall of the heart, and the initial ventricular deflections were mainly downward in the three standard leads. On March 11, 1937, the patient was admitted to Morrisania City Hospital with symptoms and signs characteristic of coronary occlusion. The electrocardiograms (Fig. 4*A*, *B*, *C*) were much the same as those obtained at Mount Sinai Hospital. In July, 1937, he entered Lincoln Hospital with still another coronary occlusion and is at present in a convalescent home.

Here, as in Case 2, the occurrence and persistence of downward initial deflections seemed to depend on the changes brought about by myocardial infarction.

CASE 6.—A 71-year-old white man suffering from diabetes, hypertension, and arteriosclerotic Parkinson's disease entered the hospital Oct. 12, 1935, with congestive failure. He gave a history of left-sided weakness, dyspnea on slight ex-

ertion of three months' duration, and occasional substernal pain during the preceding year. His electrocardiogram showed slurred, notched, widened and downwardly directed initial deflections in the three leads (Fig. 4*A*″). Roentgenologic examination revealed cardiac enlargement (hypertensive configuration) and thickening of the pleura. A month after admission he was transferred to another institution, where he died of a cerebral hemorrhage and bronchopneumonia. Permission to make a post-mortem examination could not be obtained.

The history of dyspnea and substernal pain in a patient with advanced generalized arteriosclerosis, hypertension, and diabetes mellitus suggested the possibility of coronary occlusion.

CASE 7.—A 72-year-old white woman who was known to have had hypertension for many years entered the hospital March 26, 1936, with symptoms and signs characteristic of recent myocardial infarction. An electrocardiogram revealed slurred, low-voltage QRS complexes in the standard leads, slight inversion of T_1,

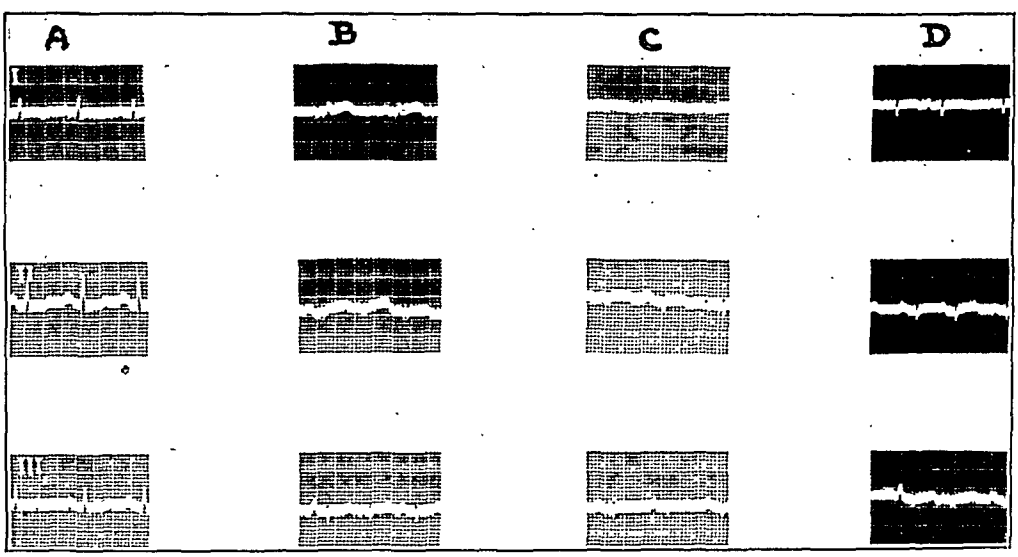

Fig. 5.

depression of T_2 and T_3, and sinus tachycardia with auricular and ventricular premature contractions (Fig. 5*A*). Bronchopneumonia developed during her first week in the hospital. An electrocardiogram made April 3, 1936, revealed very low-voltage QRS complexes (Fig. 5*B*). This low voltage persisted in the subsequent tracings, which, in addition, showed a change in configuration with the initial deflections directed downward in the three leads (Fig. 5*C*, *D*).

In this case of coronary occlusion negativity of the initial ventricular deflections in the limb leads did not appear until bronchopneumonia developed. No roentgenograms of the lungs were made, but the physical signs were not those of fluid.

CASE 8.—A 48-year-old white man entered the hospital May 18, 1937, presenting the characteristic signs of recent myocardial infarction. The electrocardiogram on admission showed evidence of marked myocardial disease, downwardly directed initial deflections, and auricular fibrillation (Fig. 6*A*). This configuration persisted

in subsequent tracings (Fig. 6*B*, *C*, *D*). Roentgenologic examination of the chest revealed fibrosis, bronchiectasis, and thickened pleura over both lungs. The patient was symptom-free on discharge, June 24. He returned two weeks later at our request. Electrocardiograms showed the same configuration as before, and were interpreted as indicating atypical bundle branch block and auricular fibrillation (Figs. 6*E*, *F*, and 7*A*). Tracings made by means of Wood and Wolferth's fourth

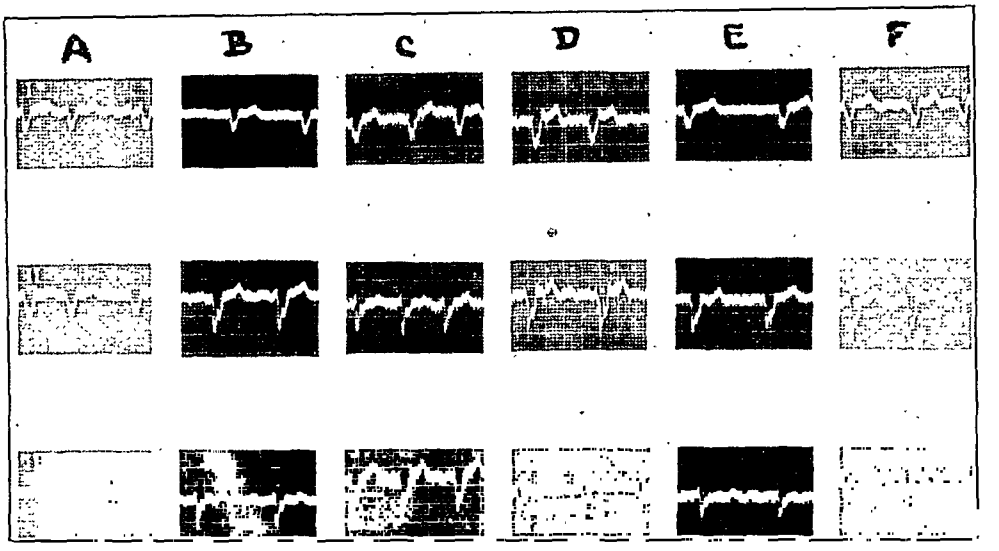

Fig. 6.

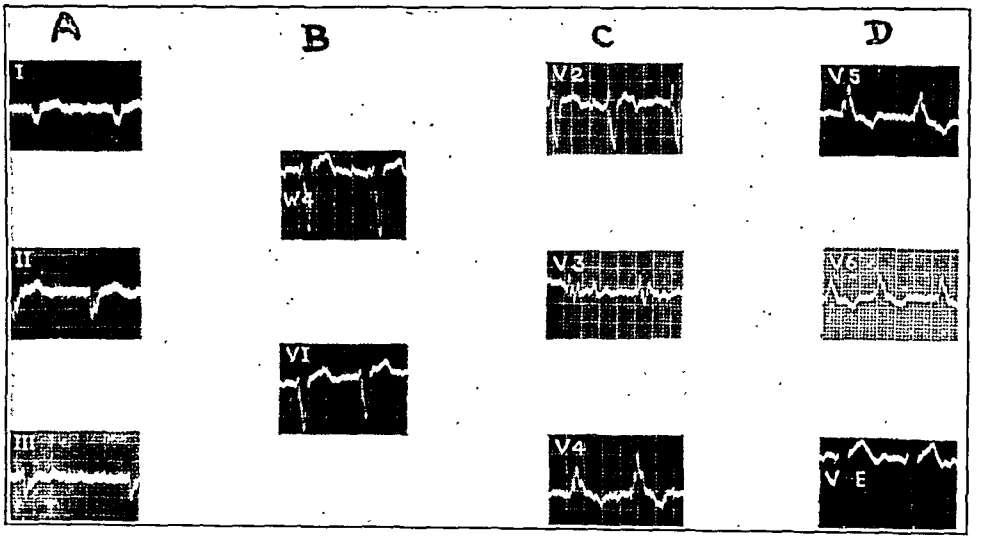

Fig. 7.

lead (Fig. 7*B*) and Wilson's precordial leads[13] (Fig. 7*B*, *C*, *D*) showed evidence of anterior wall infarction.

In this case also, the electrocardiographic changes described were apparently caused by myocardial infarction.

CASE 9.—A 38-year-old white man entered the hospital June 23, 1937, complaining of epigastric pain, swelling of the legs, and shortness of breath. He presented

the clinical signs of congestive heart failure, and five days after admission pericardial effusion became manifest. An electrocardiogram at this time was characteristic of anterior wall infarction. The main initial ventricular deflections were directed downward in the three leads (Fig. 8*A*). A subsequent electrocardiogram (July 10), made after the pericardial effusion had disappeared, revealed a return to normal configuration (Fig. 8*B*). The patient left the hospital July 12, 1937. Diagnoses: Arteriosclerotic heart disease; myocardial fibrosis, cardiac enlargement, recent coronary thrombosis; sinus tachycardia. The functional classification was III.

He was readmitted Sept. 11, 1937, in marked congestive failure with bilateral pleural effusion, ascites, and peripheral edema. In the first electrocardiograms, made a week apart, downwardly directed initial deflections were again seen in the limb leads (Fig. 8*C, D*). After disappearance of the ascites, edema, and pleural effusion, electrocardiograms again revealed normal axis deviation (Fig. 8*E, F, G*). The Q-wave (Wood and Wolferth) was absent in all of the precordial electrocardiograms which were obtained (Fig. 8*D, E, F*).

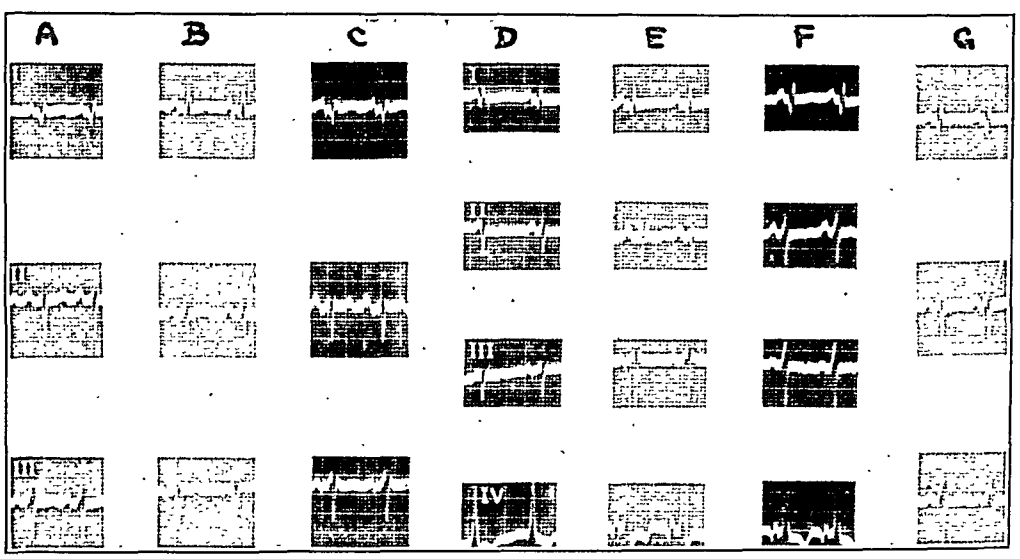

Fig. 8.

It seems likely, therefore, that in this case the edema and serous effusions were an important factor in the production of the downward deflection of the ventricular complexes.

COMMENT

These cases may be grouped according to the persistence of the downward direction of the main deflections of the ventricular complexes in the standard leads. In Cases 2, 5, and 8, this configuration was present in all records obtained. In the four cases in which this abnormality did not persist, its presence was associated with pleural and pericardial effusions. It is unfortunate that in two cases only one electrocardiogram was made.

Digitalis did not appear to have a direct effect on this abnormal configuration. It was used in two of the cases in which the negativity persisted (Cases 2 and 8). In Cases 1, 3, and 8, return to a normal configuration followed digitalization, but nevertheless the electrocardio-

graphic change seemed more directly related to the disappearance of the pleural and pericardial effusions. Digitalis influenced the electrocardiogram only to the extent to which it helped to dispel the effusions.

In view of the advanced cardiac disease present in these nine patients whose electrocardiograms showed this abnormal pattern, it is noteworthy that four of them are still alive (in Case 2, three and one-half years; in Case 5, one year; and in Cases 8 and 9, eight months, after the initial ventricular deflections were found to be directed downward). Three patients have died (in Case 6, three months, in Case 7, two months, and in Case 3, three years, after admission to the hospital). The two remaining patients (Cases 1 and 3) could not be traced.

Many problems concerning the factors involved in the production of the heart's electrical current and the conduction of this current to the extremities have not been solved, and it is therefore unwise to speculate too much regarding them. It has been pointed out that axis deviation is determined empirically,[11, 14] rather than by means of the concept of the equilateral triangle.

In our cases alterations in the electrical contacts between the heart and the conductors about it seemed to have much to do with causing the downward direction of the main deflections of the ventricular complexes in the electrocardiograms registered from limb leads, especially in those in which the configuration became normal following disappearance of pleural or pericardial effusions. This is in accord with Katz's contention[11] that fluid in the tissues surrounding the heart modifies the electrocardiogram by altering the nature of the electrical contacts between heart and body. It is interesting to note, further, that five of the patients presented clinical or roentgenologic evidence of pulmonary disease, such as bronchiectasis or thickening of the pleura, but this does not necessarily mean that changes in the heart muscle interfering with the spread of the impulse played no part in determining the form of the electrocardiogram. Eight of the nine patients had had recent coronary occlusion, and in the remaining case pericardial effusion may well have caused a certain amount of cardiac ischemia.[15]

SUMMARY

Nine cases in which electrocardiograms showed downward deflection of the main initial ventricular complexes are presented. Eight of the patients had had recent coronary occlusions, and one had pericardial effusion. In four cases this electrocardiographic abnormality seemed directly dependent upon the presence of pleural or pericardial effusion, and in the remaining cases there was evidence of chronic pulmonary disease. To produce downwardly directed initial deflections in the limb leads, it seemed necessary to have both myocardial disease causing an abnormal spread of contraction impulses, and changes in the tissues about the heart interfering with the conduction of these impulses.

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ERYTHERMALGIA (ERYTHROMELALGIA) OF THE EXTREMITIES

A Syndrome Characterized by Redness, Heat, and Pain*

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THE term "erythromelalgia," which is derived from the three Greek words *erythros* (red), *melos* (extremities), and *algos* (pain), indicates red, painful extremities (S. Weir Mitchell,[1] 1878). This term, however, is not entirely adequate because it does not denote the importance of heat. If only redness and pain were necessary for the diagnosis of erythromelalgia, such a diagnosis could be made in many cases of thromboangiitis obliterans or arteriosclerosis obliterans, for in these conditions the feet are commonly red and painful.

We propose, therefore, to substitute a more descriptive term, namely, "erythermalgia," for the syndrome commonly called "erythromelalgia." It is derived from the three Greek words *erythrotēs* (redness), *thermē* (heat), and *algos*† (pain), and therefore comprehends the three important components of the syndrome. Since we cannot apply this new term to what has already been denoted as "erythromelalgia," we have enclosed the word "erythromelalgia" in quotation marks and have used the term "erythermalgia" whenever such usage seemed appropriate.

The literature relative to "erythromelalgia" is very confusing. Many cases have been reported as examples of "erythromelalgia" which bear only the slightest resemblance to the condition. Part of the confusion results from the fact that in earlier times reliable methods of determining the temperature of the skin were not available and part from the lack of a precise definition, which, as Lewis has pointed out, was evident even in Mitchell's original presentation. The literature on the subject was reviewed by Cassirer[2] in 1912, and by May and Hillemand[3] in 1924. Since the latter date little of importance has been published except the reports of Brown,[4] Lewis,[5] and Mufson.[6]

At the risk of seeming to hold the past literature on "erythromelalgia" too lightly, we propose to delineate the clinical, thermometric, and physiologic manifestations of a clinical syndrome which we have ob-

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†We have used the term *erythrotēs* to designate the discoloration observed in this syndrome. It varies widely in intensity in different cases. In appearance, it varies from a dusky or cyanotic redness to a light redness. Usually it is the least remarkable of the three constituents of the syndrome. The term *therm* is used to indicate heat or excessive warmth. Although the chief attribute of this term lies in its indication of objective warmth or heat, it may also express subjective warmth or heat. The term *algos* indicates pain of a nonspecific nature which is less tolerable than mere discomfort.

served on several occasions and which we have designated "erythermalgia." This condition is characterized by burning distress, involving any of the extremities, which is inseparably linked with, and entirely dependent on, elevation of the temperature of the skin of the affected parts. When the temperature of the skin is elevated to or above a certain critical level by any means, distress occurs, and when the temperature of the skin is reduced, by any means, to a point below the critical level, the distress disappears. This condition affects otherwise healthy persons who do not have any detectable organic disease of the nervous or vascular systems, and it may therefore be considered a primary disturbance.

Occasionally the syndrome may be associated with hypertension or polycythemia, and it may occur in organic neurologic or vascular disease, but under these circumstances it seems to be a secondary manifestation of the organic disease. Whether primary or secondary, however, the syndrome is essentially the same. An analogous situation holds in Raynaud's syndrome, for vasomotor symptoms similar to those observed in Raynaud's disease may occur in thromboangiitis obliterans, arterial thrombosis due to cervical rib, and in a variety of other conditions which do not warrant the designation "Raynaud's disease" because the vasomotor syndrome is obviously secondary to organic disease. We are not concerned here with Lewis' observation that the syndrome may involve areas other than the extremities.

PATHOLOGIC PHYSIOLOGY*

Increased Temperature of the Skin.—An increase in the temperature of the affected extremity in erythermalgia is invariably accompanied by distress. It makes no difference whether the increase occurs spontaneously or is induced by local application of heat, as by immersing the extremity in warm water, increasing the temperature of the environmental air, or warming the skin by direct contact with a warmed metal bar.

Of all the various disturbances occurring in erythermalgia the increased temperature of the skin is the most important, and it is entirely constant. The temperature at which distress can be produced varies with different individuals and in different parts of the extremity of the same individual. It usually lies within the range from 32° to 36° C. Lewis' designation, the "critical point," is an excellent one; it indicates the temperature at which distress occurs. With temperatures higher than this critical point the distress persists, and with temperatures below this critical point the distress disappears. Lewis has justifiably objected to the intimation that increased temperature occurs in episodes indicative of "vasomotor storms," for the increased temperature and hence the distress may be reasonably constant as we will show later in the report of cases.

*For the purpose of clarity we have simplified this phase of the presentation and intentionally avoided detail.

Vasodilation.—Vasodilation is the most common cause of the increased temperature of the skin in erythermalgia. It seems to be the direct cause of the attacks of burning distress which occur spontaneously. Vasodilation, however, is only an indirect and not an integral part of the mechanism causing the distress. This is shown by the observation that distress can be induced by warming the skin of an extremity affected with erythermalgia, or it can be maintained in such an extremity when the flow of blood has been brought to a standstill by inflation of a cuff about the extremity to a pressure greater than the systolic blood pressure, provided the warmth of the skin is as great as, or exceeds, the critical point. Evidence of vasodilation other than increased temperature of the skin is increased amplitude of arterial pulsation, the throbbing sensations that are frequently mentioned by patients, increased elimination of heat (as shown by calorimetric studies), and increased content of oxygen in the venous blood coming from the extremity.

Hydrostatic Pressure.—If the temperature of the skin is just slightly below the critical point, distress may be induced when the intravenous pressure is increased by placing a sphygmomanometer cuff about a proximal joint of the extremity and inflating it to a pressure about the same as the diastolic blood pressure. In addition, distress may be lessened if an extremity is elevated, and accentuated if an extremity is dependent, even if the temperature of the skin remains unchanged. The burning distress may be relieved by direct pressure on the skin. We cannot agree with Mufson that the fundamental cause of the distress in erythermalgia is relative hypertension within the minute vessels of the skin, for, if the temperature is suitably increased, distress may be induced in an extremity in which blood flow has been stopped.*

Susceptible State of the Skin.—It is apparent on even superficial consideration that temperatures of the skin which almost routinely† provoke distress in patients with erythermalgia have no such effect on those without erythermalgia. This observation caused Lewis to describe a "sensitive state of the skin." It seems unquestionably true that, for reasons not clearly understood, the skin in erythermalgia is sensitive in an unusual degree to warmth.

Vasoconstriction.—In some instances there seems to be unusual vasoconstriction in the extremities between episodes of burning distress. This is shown generally by hypertension (in two of our cases) and locally by coldness and cyanosis or pallor of the skin between the episodes of burning. Furthermore, two of our patients had hypertension.

*By means of inflation of a sphygmomanometer cuff about a proximal joint.

†We have noted a "resistant phase" in patients with erythermalgia. If high temperature of the skin and distress are produced repeatedly, a transient period may be reached in which an increase in the temperature of the skin is not associated with distress.

NATURE OF THE DISTRESS

Mitchell's "pain of a burn," "pain of mustard," and "pain of intense sunburn," are graphic descriptions of the severity and character of the pain. The patient usually states that the distress affects the ball of his foot or the tips of his toes, or the corresponding parts of the hand. However, as one induces distress for purposes of study, it is often described vaguely by the patient as an aching, pricking, sticking, pins-and-needles sensation which may not be localized at all and which may extend up past the ankle or, as it becomes more severe, may reach the knee or even the hip. This type of pain is not burning until the critical level of temperature is exceeded. Moreover, it is fluctuating in type, rising in increasing waves, with shorter and shorter intervals between crests, until it passes from the sticking, pricking type of pain into a definitely burning distress. A modified form of this pricking stage may be noticed as the extremity cools below the critical temperature.

DIAGNOSIS

A diagnosis of erythermalgia is justified provided there is close correlation between temperature of the skin and the distress. While there may be other manifestations, such as those mentioned in the preceding paragraphs, the dependency of distress on the temperature of the skin is characteristic and pathognomonic of erythermalgia. Sensations of burning in the extremities such as are commonly noted by patients with arteriosclerosis and peripheral neuritis, for example, do not indicate erythermalgia. While close questioning of an intelligent, observing patient who has noted objective absence or presence of increased warmth of the skin when burning distress occurs may allow tentative exclusion or acceptance of the diagnosis of erythermalgia, the final diagnosis must be based upon objective studies.

METHODS OF STUDY*

In order to demonstrate the essential relationship between skin temperature and distress, it is necessary to increase the temperature of the skin to a value at which distress occurs. This can be accomplished in several ways: 1. Reflex vasodilation can ordinarily be accomplished by means of a baker containing five or six carbon filament lamps so supported that they are about 18 inches (46 cm.) above the skin of the abdomen and chest. A blanket is placed over the baker and the feet are exposed to room air. The temperature of the air within the baker usually is between 50° and 60° C. Sometimes simply wrapping the extremities in blankets will cause an adequate increase in the temperature of the skin. 2. Direct warmth can be applied by enclosing the extremity within a rough blanket tent, within which a lighted carbon filament bulb is placed.

*In all of these studies the temperature of the skin was measured by Sheard's electric thermocouple.[7]

For some reason we have not had much success in producing the distress by immersing the extremity in warm water. The reason for this is not clear. A cylindrical copper bar, about 1 inch (2.5 cm.) in diameter, may be warmed to the desired temperature by immersion in water and applied directly to the skin. Whenever these methods are used, distress is more easily induced when the extremity is dependent. The explanation for this is presented in the paragraph on hydrostatic pressure.

If erythermalgia is present, burning distress occurs as the temperature of the skin increases. Ordinarily, burning occurs when the temperature of the skin is increased to about 32° C., and this burning increases in intensity as the temperature of the skin is still further increased. If the mechanism for increasing the temperature of the skin of the extremity is removed and the temperature decreases, the distress disappears. Ordinarily, the critical point of temperature varies less than 1° C. in repeated experiments, although different patients have somewhat divergent critical points. If distress is induced repeatedly, a resistant phase may occur, during which distress cannot be produced even though the temperature of the skin is increased satisfactorily. If the distress is proved to be dependent upon the temperature of the skin, the diagnosis of erythermalgia is established. Confirmatory findings are an increase in the distress when the extremity is dependent or when the venous pressure is raised by means of a sphygmomanometer cuff, and a decrease in the distress when the extremity is elevated or immersed in cold water.

REPORT OF CASES

CASE 1.—A white man, a foreman of underground construction in a gold mine, aged 31 years, registered at the Mayo Clinic in September, 1937. In February, 1936, a falling rock had caused a chip fracture of the bone of the left great toe, from which recovery was prompt. In January, 1937, for a short time pain in the left great toe and foot, associated with some swelling of the foot, caused limping. The patient felt that the resultant distress was not the same as that which he experienced subsequently. In July, 1937, this latter type of distress, which will be described subsequently, appeared, and as a result the fragment of bone was removed from the left great toe. Relief was not experienced except while the patient was in bed.

From the time of onset in July, 1937, to the time of the patient's admission to the clinic, he had experienced eight attacks of distress, each of which lasted three or four days. At first, only the left great toe was involved, but in the last two attacks the discomfort spread to the ball of the foot and the fifth toe. This distress was described as "hot, burning, throbbing, aching and pulsating" in nature. It seemed to be precipitated and aggravated by work, walking or climbing. Relief was obtained constantly but transiently by rest, elevation, and cold water. Some medicine, which the patient believed to be sodium salicylate, had not helped. Because of the distress the patient was forced into a sedentary occupation. While he was driving to Rochester he discovered that 10 grains of acetylsalicylic acid (aspirin) produced

prompt relief, which persisted for about three days. He had noted increased surface temperature, red to deep purplish discoloration, and increased sweating of the foot during episodes of distress.

Physical examination and routine laboratory tests gave negative results. The peripheral arteries pulsated normally. The percentage volume of cells in the blood (hematocrit) was 53.0.

The patient lay on a bed in a room which was kept at a constant temperature, fully clothed except that his shoes were removed, for forty minutes. His socks were removed at 1:55 P.M., and he lay with his feet exposed until 2:25 (Table I). No

TABLE I

TEMPERATURE STUDIES (CASE 1)

TIME P.M.	TEMPERATURES IN DEGREES C.								ROOM TEMP. C.
	LEFT FOOT				RIGHT FOOT				
	FIRST TOE	THIRD TOE	FIFTH TOE	BALL OF FOOT	FIRST TOE	THIRD TOE	FIFTH TOE	BALL OF FOOT	
2:05	30.4	31.2	30.1	33.8	28.2	29.2	30.5	30.9	24.7
2:25	30.5	31.4	30.7	33.7	27.1	28.9	29.7	30.4	24.3
2:27	31.2*	31.9	31.1	34.1*	27.1	29.0	30.1	30.4	24.1
2:35	32.4*	34.0*	31.9*	34.8*	27.7	29.8	30.7	30.3	23.7
2:41	32.6*	34.6*	33.2*	35.1*	29.3	30.3	31.2	30.5	24.6
2:55	32.3*	34.2*	32.2	35.4*	30.3	29.8	31.0	30.8	23.9

*In this and subsequent tables this designation (*) indicates the presence of distress.

distress was noted. At 2:25 he sat on the edge of bed with both feet dependent. Distress of a "throbbing" type involved the left first toe and the outer side of the left foot in about twenty-five seconds. The temperature of the left foot increased rapidly, and, as it did so, "aching," "burning," and "soreness" occurred in the distal half of the foot. Changes in the temperature of the skin of the right foot were minimal (Table I). On a subsequent day, during an episode of spontaneous distress associated with an elevated skin temperature, the patient was given 10 grains

TABLE II

TEMPERATURE STUDIES (CASE 1)

TIME A.M.	TEMPERATURES IN DEGREES C.						ROOM TEMP. C.	COMMENT
	LEFT FOOT			RIGHT FOOT				
	FIRST TOE	THIRD TOE	BALL OF FOOT	FIRST TOE	THIRD TOE	BALL OF FOOT		
9:30	23.8	23.2	24.6	23.4	23.1	24.3	23.4	Patient recumbent
9:40	23.8	23.1	24.6	23.3	23.1	24.2	24.3	Patient recumbent
9:42	23.8	23.2	24.6	23.3	23.1	24.2	24.1	Patient sitting; feet wrapped in blanket
10:30	25.4	24.2	25.6	23.4	23.4	24.3	24.0	Patient sitting; feet wrapped in blanket
10:47	29.4	26.3	27.5	23.9	23.4	24.4	24.4	Heat applied to blanket
11:15	32.7	32.0	32.2	24.2	23.5	24.7	24.0	Heat in blanket
11:35	36.9	33.0	34.5	31.5	27.5	28.8	24.2	Heat in blanket
11:45	38.1	33.9	35.0	35.4	35.5	30.3	24.0	Heat removed
11:50	36.0	33.2	34.9	35.0	29.0	30.6	23.9	Heat removed
12:00	35.1	34.0	34.8	32.8	28.8	30.7	24.0	Heat removed

of acetylsalicylic acid by mouth. Complete relief was experienced in twenty minutes, although the skin temperature was not influenced by the drug. It was also shown that immersion of the foot in cold water gave immediate relief. Additional studies showed that vasodilation was more easily induced in the afflicted areas than elsewhere. When both feet were wrapped loosely in a blanket, within which heat was produced by a carbon filament bulb, the temperature of the skin of the left first and third toes and of the ball of the foot increased more rapidly than did that of corresponding areas of the right foot (Table II). This procedure, carried out two or three days after the patient had ingested aspirin, did not produce distress even though the temperature of the skin was high.

These observations seem to us to be important. As expected, there was a close relationship between the distress and the temperature of the skin. The critical point was from about 31.0° to 32.0° C. Most surprising was the marked increase in the temperature of the skin of the left foot as a result of dependency alone; in contrast, there was very little change in the temperature of the right foot. Noteworthy also was the prompt relief following the administration of acetylsalicylic acid.

CASE 2.—A 30-year-old Polish Jewess registered at the clinic April 21, 1937. She complained of burning of the feet which had been present for twelve months. Twenty months before she had noticed an aching weakness in her feet and the lower part of her legs while standing in street cars. Many treatments had been tried without relief. She came to the United States in April, 1936, at which time the typical distress appeared. She described it as a severe burning and pricking sensation which involved both feet. The distress was made worse by wearing shoes, hot weather, walking, standing or sitting, and she had noticed that it occurred after a warm bath. She had obtained relief by bathing or swimming in cold water, by walking on cold floors, and by elevating her feet. When the distress was present, her feet felt swollen, appeared puffy and red, and felt quite hot to the touch. She slept with few covers and often uncovered her feet, even in cold weather. There was always a definite relation between the burning distress and the objective temperature of the feet. She found she could walk four or five blocks in cold weather, but only one block in warm weather, before the burning distress appeared. General physical and neurologic examinations gave essentially negative results. Routine laboratory studies did not disclose any abnormality.

The patient lay in a room with a constant temperature for an hour and her shoes and stockings were then removed and she sat up (Table III). There was some in-

TABLE III

TEMPERATURE STUDIES (CASE 2)

TIME P.M.	TEMPERATURES IN DEGREES C.					ROOM TEMP. C.	COMMENT
	LEFT FOOT			RIGHT FOOT			
	FIRST TOE	THIRD TOE	BALL OF FOOT	FIRST TOE	BALL OF FOOT		
3:00	27.1	28.2	28.2	28.3	29.2	27.5	Patient sitting
3:08	31.7	28.9	30.4	32.0	30.9	27.4	Feet covered with blanket
3:19	34.6*	31.7*	32.4*	34.8*	32.6*	27.3	Feet covered with blanket
3:23	35.5*	34.0*	34.7*	35.4*	34.5*	27.4	Feet covered with blanket
3:29	35.4*	34.1*	34.9*	35.3*	35.0*	27.5	Feet covered with blanket
3:32	35.1*	33.8*	35.0*	35.2*	35.3*	27.4	Feet covered with blanket
3:34	35.1*	33.7*	35.1*	35.1*	35.7*	27.5	Feet covered with blanket

crease in the temperature of the skin, and this was accelerated when the feet were wrapped in a blanket. As the skin temperature increased, burning distress occurred and persisted as long as there was any elevation of the surface temperature. When the distress was most marked, it involved not only the feet but the legs as well. Elevation of the feet above the horizontal caused immediate lessening of the distress; placing them again in the dependent position caused it to recur with maximal intensity. Standing increased the distress still more. When the distress in the feet was marked, they appeared swollen, the skin was very dusky red, hyperhidrosis was present, and the pulsation of the arteries was visibly increased. Pulsation of the veins was not noted. Immersion of the feet in cold water gave prompt relief.

As in Case 1, there was a distinct relation between the temperature of the skin and the distress. Also, vasodilation was induced with unusual ease. Elevation of the feet caused an immediate amelioration of the distress without significant change in the temperature of the skin; dependence of the feet caused an accentuation of the distress. Again, prompt relief was noted on immersing the feet in cold water.

CASE 3.—A woman, 50 years old, was examined at the clinic in January, 1937. Burning distress had affected her feet for five years. When the distress occurred while she was wearing shoes, there was a sensation of "muscular cramping"; this was relieved by massage and walking. The distress was caused by exposure to warm air, or by wearing wool stockings or overshoes indoors. The patient traveled much by automobile and train and had noted that distress was caused by unusual warmth in trains and from the engine when motoring. In warm weather the distress was worse. She had obtained relief by removing her shoes and putting her feet out the window of the automobile while motoring, by walking on tile floors, by wearing sandals, and by immersion of the feet in cold water. When the distress occurred at night, uncovering the feet gave some relief. While she had made no exact observation relative to skin temperature, she had noticed that her feet were unusually warm when the distress occurred while motoring. She had never noticed discoloration of the skin but her feet seemed swollen when the distress was present. This was indicated by a "puffy" feeling and by the tightness of her shoes.

Physical examination and routine laboratory tests gave negative results. The blood pressure was 124/76. The arteries of the feet pulsated normally. With the patient lying on a bed, covered by a sheet, a baker was applied to the trunk. Vasodilation occurred in the feet, and, as the temperature of the skin increased, the burning distress occurred (Table IV). Soon after the heat from the baker was

TABLE IV

TEMPERATURE STUDIES (CASE 3)

TIME A.M.	TEMPERATURES IN DEGREES C.						ROOM TEMP. C.	COMMENT
	LEFT FOOT			RIGHT FOOT				
	FIRST TOE	THIRD TOE	BALL OF FOOT	FIRST TOE	THIRD TOE	BALL OF FOOT		
9:50	24.4	24.7	27.3	24.4	24.4	27.0	24.9	Patient lying
9:56	24.7	24.8	27.3	24.8	24.6	27.0	25.0	Heat to trunk
10:13	29.5	30.7	31.9*	31.5	27.5	31.2*	24.5	Heat to trunk
10:39	33.3*	33.2	35.4*	34.3*	32.0	35.2*	24.7	Heat to trunk
10:47	34.0*	34.0	35.8*	34.8	32.7	35.5*	25.0	Heat removed
10:58	33.9*	33.8	35.6*	34.9*	33.2	35.5*	24.8	
11:07	33.3	33.2	35.2*	34.0	32.9	35.0*	25.1	
11:25	28.3	28.2	29.2	28.4	27.7	29.1	23.8	

turned off, the temperature of the skin of the feet decreased and the distress disappeared. This study was repeated twice with the same results. At another time, when the temperature of the skin was just below the critical point and distress was absent, the inflation to 60 mm. of a sphygmomanometer cuff placed about the calf caused prompt burning. On several occasions a copper bar about 1 inch (2.5 cm.) in diameter was warmed in water to about 45° C. When it was placed against the skin for from thirty to forty-five seconds in an area in which distress had been present previously, distress was promptly induced. The temperature of the skin in contact with the bar increased by about 2° C. When the bar was removed, the temperature decreased and burning disappeared. Blood drawn from a vein over the internal malleolus of the right foot when burning was present and when the temperature of the skin of the ball of the right foot was 34.0° C. was 91 per cent saturated with oxygen. When burning was absent and the temperature of the ball of the right foot was 22.8° C., the venous blood was 69.0 per cent saturated.

CASE 4.—A woman, 45 years old, was admitted to the clinic on Jan. 25, 1937. For many years her employment had consisted of sewing and pressing, or capping bottles, and this had required much use of her feet and at times had subjected them to considerable vibration. Her work fatigued her unduly, and she slept poorly. Beginning in 1924, for two or three years, while she was employed at packing objects in excelsior, her finger tips had "burned" and were "red," so that eventually she was forced to give up this kind of work. In the five or six years preceding her admission she noticed painful burning distress in both feet, but particularly the right. The distress involved chiefly the skin over the balls of the feet and toes, especially the right fifth toe. Sometimes a "crawling, tingling" sensation and aching were noted. The distress was accentuated or precipitated by a warm bath, wearing shoes, using an electric sewing machine, and by covering the feet in bed. Relief was experienced by exposing the feet to cool air, by the application of cold, wet towels, walking barefoot on cool floors, and by immersing the feet in cold water. The patient had noticed that one tablet of acetylsalicylic acid or of anacin produced relief in about twenty minutes which persisted for days. Early in the course of the disease she required one tablet of either of these drugs about every month, but during the period immediately before admission to the clinic half a tablet had been required every three or four days. The fact that she had hypertension had been known for three years. For a similar period there had been transient bluish discoloration, chiefly of the right and left first and fifth toes.

Examination revealed hypertension (the blood pressure varied from 220/120 to 140/105), a barely palpable spleen, and localized areas of mottled cyanosis from 2 to 3 cm. in diameter, one of which was on each buttock and one over the left iliac crest. There was a lymph node about 1 cm. in diameter in the left axilla, and the scar of simple amputation of the right breast. At the time of the first examination the patient's feet appeared normal when she lay down. On dependency, deep cyanosis involved both fifth toes, particularly the right, and the lateral edges of the dorsa of the feet proximal to the fifth toes. There was blotchy cyanosis of the plantar surfaces of both great toes and slight cyanotic discoloration of the soles of both feet. Neurologic examination gave negative results. The usual laboratory tests were negative save for albuminuria, a slight increase in the transverse diameter of the heart on roentgenologic examination, and a basal metabolic rate of +19.0 per cent. There was no evidence of polycythemia. The leucocytes numbered 13,200 per cubic millimeter; 12 per cent were lymphocytes, and 87 per cent neutrophils.

While the patient was under our observation, the discoloration of the feet increased and became more constant, even when they were warm. The peripheral arteries pulsated normally. Because the areas of discoloration suggested hemangiomas somewhat, a clinical diagnosis of Kaposi sarcoma was considered. A discolored

area on the sole of the left foot was excised for microscopic study, but there was no evidence of hemangioma or sarcoma. In February, 1937, ulceration occurred on the tip of the right fifth toe. On February 10 and 11 roentgen treatment* was given to the dorsum of the right foot and dorsum of the left foot, respectively, and on February 12 to the buttocks. The patient was dismissed on February 17. She returned to the clinic March 29, 1937. The burning distress of which she complained originally had entirely disappeared from the right foot; on the left side it was present to a slight degree in the ball of the foot and in the fifth toe. There was less ulceration of the right fifth toe than at the time of previous dismissal, but the patient had not been active. Her feet were normal in appearance when in the horizontal position except for some cyanosis of the left fifth toe. When the feet were dependent, discoloration occurred as at the time of the first examination, but more slowly.

At the time of the first examination studies were carried out to determine the relationship of the temperature of the skin to the distress (Table V). These studies

TABLE V

TEMPERATURE STUDIES (CASE 4)

TIME P.M.	TEMPERATURES IN DEGREES C.							ROOM TEMP. C.	COMMENT
	RIGHT FOOT				LEFT FOOT				
	FIRST TOE	THIRD TOE	FIFTH TOE	BALL OF FOOT	FIFTH TOE	BALL OF FOOT	DORSUM OF FOOT		
3:48	32.1	34.0	29.6	36.0	32.0	34.4	35.3	24.8	Standing
4:09	32.2	34.6	29.9	35.3	31.2	34.1	34.8	25.6	Blanket around feet; patient recumbent
4:14	32.8	35.0	30.4	35.8	32.3	34.7	35.2	25.9	Blanket around feet; patient recumbent
4:18	34.9	36.1	31.4*	36.1	34.0	35.0	35.8	25.8	Blanket around feet; patient recumbent
4:25	36.3	36.7	32.7*	36.5*	34.9	35.2	36.3	25.5	Blanket around feet; patient recumbent
4:30	36.9*	37.0*	34.0*	36.9*	35.0	35.1	36.9	25.3	Blanket around feet; patient recumbent
4:47	37.0	37.0*	35.2*	36.3*	34.8	35.1*	37.3	24.9	Blanket around feet; patient recumbent
5:00	36.8	37.0	35.5*	36.5*	34.8	35.3	36.3	25.7	Blanket removed
5:10	36.0	36.3	35.2*	36.2*	33.6	34.8	35.6	25.6	
5:20	32.1	32.3	31.2	35.4	31.1	34.4	34.9	25.6	

showed that vasodilation was induced simply by wrapping the feet in a blanket. The critical point was found to be high for the right first and third toes and for the balls of the feet. Distress did not affect the left fifth toe or dorsum of the left foot. At another time the patient was studied in a room in which the temperature of the environmental air was low (19.2° C.). Vasodilation was induced with difficulty by means of a baker placed over the body until the feet were wrapped, when vasodilation occurred rapidly. Studies were carried out on several occasions. The critical point for any area varied considerably and the ease with which vasodilation could be induced varied greatly. In all studies, however, there was a definite relation between the distress and the temperature of the skin. Burning never occurred unless the temperature of the skin was elevated.

When the patient returned to the clinic the second time, vasodilation was induced by a body baker and by a blanket placed around the feet. Distress occurred only in the areas in which it had occurred spontaneously between the time of her first

*135 kilovolts, 16 inches distance, 5 milliamperes, 4 millimeters aluminum filter, 16 minutes.

dismissal and readmission, that is, in the left fifth toe and ball of the left foot. The temperature of the skin of the right fifth toe, for example, increased to 35.3° C. without causing distress.

This case was puzzling throughout. The symptoms of erythermalgia were definite, but the appearance of the feet was unusual. The situation was further complicated by the presence of hypertension, a palpable spleen, elevation of the basal metabolic rate, and by the presence of discolored areas on the buttocks. In addition, the patient was a poor observer, and at times the distress was so great that she could not cooperate. While in almost every way this is the least satisfactory of the five illustrative cases, on repeated study it was apparent that there was sufficient correlation between elevation of skin temperature and the occurrence of symptoms to justify the diagnosis of erythermalgia.

CASE 5.—A man, 48 years old, was examined at the clinic in December, 1930, because of pains in his arms and chest, weakness, nervousness, poor memory, and dizziness. The value for hemoglobin was 17.8 gm. per 100 c.c., and the erythrocytes numbered 4.7 millions per cubic millimeter. The diagnosis was anxiety neurosis. The patient returned to the clinic in August, 1936, when the symptoms just mentioned had to a large extent disappeared. For two years he had noticed burning distress involving various areas of the skin of his right foot, chiefly the plantar surface and first toe. Reddish discoloration of the foot had also been present. The distress, which was fairly constant, was made worse by walking, which also increased the discoloration and the cutaneous temperature. The patient was finally forced to walk with a cane. Relief from the distress was experienced on elevation of the foot. Immersion in cold water had not been tried.

On examination, there was an unusual redness of the skin of the face, cyanotic discoloration of the buccal mucosa, and increased reddening of the conjunctiva. The entire right foot was dusky red and obviously warmer than the left. The veins of the right foot were distended. The liver and spleen were slightly enlarged to palpation, and the heart was slightly enlarged to percussion. The blood pressure was 178/112. The value for hemoglobin was 20.9 gm. per 100 c.c., and the erythrocytes numbered 5.13 millions per cubic millimeter. The percentage of cells in the whole blood (hematocrit) was 66, and the whole blood volume was 8,009 c.c., or 109 c.c. per kilogram of body weight. The value for blood uric acid was 3.7 mg. per cent. The respective temperatures of the skin of the right first, right third, left first, and left third toes in degrees centigrade were 31.9°, 32.1°, 27.6°, and 26.8°. Blood taken from a vein on the dorsum of the right foot contained 24.5 volumes of oxygen per 100 c.c. (91 per cent saturation), whereas that drawn from a vein on the dorsum of the left foot contained 18.7 volumes of oxygen per 100 c.c. (69.5 per cent saturation). There was roentgenologic evidence of osteoporosis of the right foot. A diagnosis of polycythemia vera and erythermalgia was made.

Because of financial reasons, the patient returned to the care of his local physician, who on four occasions performed venesection. A year after the patient had been dismissed from the clinic his physician wrote that the patient no longer had distress in his right foot.

Examination of the patient and of his blood established the diagnosis of polycythemia vera. All the criteria of erythermalgia were satis-

fied, namely, reddish discoloration, increased temperature of the skin, and the characteristic burning distress. At the clinic, the relationship between erythermalgia and polycythemia has become so firmly established that polycythemia is suspected when there are symptoms suggestive of erythermalgia.

Most interesting was the finding of the high concentration of oxygen in the blood taken from the vein on the dorsum of the right foot. The content of oxygen in this venous blood approached that normally found in arteries. This phenomenon was noted previously by Brown,[4] who considered it as evidence of a high degree of vasodilation. Another explanation which occurs to us is the functioning of the arteriovenous anastomoses which normally are not functioning, or are functioning to a less degree. Such an hypothesis would help to explain the dusky redness of the skin, indicating a low oxygen content of the capillary blood while at the same time there was a high concentration of oxygen in the venous blood. In other words, blood may have been shunted directly from the arterioles to the veins.

One of the objections to accepting polycythemia as the cause of the erythermalgia was the unilaterality of the latter condition. Since the disturbances in circulation resulting from polycythemia are bilateral, one might reasonably expect erythermalgia to be bilateral. However illogical it may seem, there is, in our experience, a direct cause and effect relationship, for a return of the blood to normal may cause the disappearance of unilateral erythermalgia. It may be that one extremity has some inherent susceptibility not present in the other. Unfortunately we can only assume, and not be entirely certain, that in the case under discussion relief of the polycythemic state was responsible for the disappearance of the erythermalgia. We see no difference between the syndrome noted in this case and that which occurs primarily, except that the distress was more constant, apparently because the cause of the vasodilation was persistent.

TREATMENT

The treatment of erythermalgia is not uniformly successful, as was observed originally by Mitchell[1] and emphasized by Brown.[4] It is, of course, important to determine whether there is any condition such as polycythemia to which erythermalgia might be secondary. Under such a circumstance the treatment of the syndrome affecting the extremities would be the treatment of the condition which produces it. Surprisingly, acetysalicylic acid in amounts of as little as 10 grains (0.65 gm.) may produce marked relief which persists for as long as several days. No adequate explanation of this is available, but it is so common that we have learned to suspect erythermalgia whenever patients mention marked and prolonged relief as a result of using this drug.

Mufson[6] noted marked relief following the injection or inhalation of solutions of epinephrine chloride. He believed that the distress of erythermalgia was a manifestation of relative hypertension in the minute vessels of the skin, a condition which epinephrine relieved. We have not had enough experience with this method of treatment to justify an opinion as to its efficacy.

Some symptomatic relief may be obtained by avoiding procedures that produce vasodilation in the extremities. Residence in a moderate climate may help. Avoidance of exposure of the feet to warmth, as in riding in the front seat of an automobile, may alleviate some of the distress, as may also the use of light socks or stockings and of sandals or perforated shoes.*

When simple measures fail, it may be necessary to anesthetize the skin of the feet by section, crushing, or by the injection of alcohol into such peripheral nerves as the posterior tibial, peroneal and sural. A logical method is to attempt to desensitize the skin to warmth. At first, the extremities should be immersed in water at 30° C. for fifteen minutes twice daily for two or three days. The temperature of the water should then be increased one or two degrees for another period of two days, and this program should be continued. If distress occurs when the temperature of the water is that which ordinarily provokes distress, the treatment should be begun again. If this plan of treatment is successful, the water at the temperature which provoked distress before the treatment was begun will not cause distress. As yet we have no evidence that this plan of treatment is helpful.

SUMMARY

A clinical syndrome has been described which was designated "erythromelalgia" by Mitchell and for which we suggest the term "erythermalgia," thus indicating its three important components, namely, redness, heat, and pain. This syndrome, which may affect one or more extremities, is characterized by discoloration and distress, both of which are dependent entirely upon the temperature of the skin, the increase of which constitutes the third component. The condition may occur as a primary disturbance, or it may be secondary to such conditions as polycythemia vera.

The diagnosis depends on the establishment of a close relationship between the occurrence of the distress and the temperature of the skin. When the temperature of the skin increases above a critical point, the distress occurs; when it decreases below the critical point, the distress disappears. The distress itself results from a susceptible state of the

*Treatment of the painful areas with roentgen rays or radium may help. Such treatment should, of course, be carried out only by an expert.

skin to increased temperatures, a condition which does not occur in normal persons. The diagnosis is relatively simple; the treatment may be unsatisfactory.

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STUDIES OF THE CIRCULATION IN PERICARDIAL EFFUSION*

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THE function which the pericardium serves has not been sharply defined. The notion is current that its chief function is to prevent rapid dilatation of the heart.[1] Too much emphasis has been placed on this point, for congenital absence of the pericardium occurs in man, and an analysis of the case histories of patients who exhibited this defect did not indicate that they had suffered circulatory embarrassment.[2, 3] Moreover, in dogs, the pericardium may be excised without giving rise to untoward effects.[4] Indeed, it has been our experience,[5] as well as that of others[6, 7, 8] that patients suffering from Pick's syndrome may be "cured" by the excision of a constricting adherent pericardium. The pericardium is a none too distensible sac when subjected to rapid stretching, but is capable of rather remarkable distensibility when the pressure is applied slowly. The diseases to which it is subject give it unusual significance even though its exact functions have not yet been defined. On the one hand, there are the lesions which give rise to pericardial effusion, and, on the other hand, those leading to the formation of adhesions, which may be external or internal, or both. In fact, the first, fluid may be the forerunner of the second, adhesions. In both situations the function of the enmeshed organ, the heart, may be seriously impaired. Because pericardial effusion occurs frequently in the course of rheumatic infection, tuberculosis, and empyema, as a consequence of other infections involving its surfaces, in uremia, and occasionally in congestive heart failure, there is point in knowing to what extent it interferes with the circulation. Fluid may be present in sufficient quantity to give rise to cardiac tamponade. Cohnheim[9] described with clear finality certain circulatory consequences of acute distention of the pericardium in animals. As a matter of fact, the information which is available has been derived for the most part from observations made on animals. Patients with pericardial effusion are too ill in most instances to cooperate in prolonged and detailed observations. The pericardial cavity with its film of fluid between its outer (parietal) layer and its inner (visceral) layer no doubt contributes to the smooth motion of the heart during contraction, and for this there may be an optimum amount of fluid. However, the mechanism of the formation and absorption of pericardial fluid and the factors controlling its quantity under normal circumstances are not precisely known.

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We have had the opportunity of making certain observations which help to solve these puzzling problems.

For 24 months we have had under observation a patient (E. C., History 94114) suffering from recurrent chronic pericardial effusion which appeared to be a primary lesion. The patient was not acutely ill, had no fever, and attended school in the intervals between therapeutic pericardial taps. After prolonged observation it became apparent that slowly developing cardiac tamponade was responsible for the patient's pleural effusion, ascites, and hepatic enlargement, for removal of the pericardial fluid resulted in improvement, as shown by collapse of distended veins and decrease in dyspnea, pleural effusion, ascites, and edema of the face and of the lower extremities. The improvement began immediately and continued for a week to ten days. The patient's condition then remained approximately unchanged for a week to ten days, following which there was a gradual recrudescence of the signs and symptoms as the pericardial fluid increased in sufficient amount to embarrass the circulation. For 24 months, paracentesis has been necessary at monthly intervals. The appearance of the consequences of the pericardial obstruction (edema, ascites) might be delayed by administering salyrgan or mercupurin intravenously at intervals of seven to ten days after a tap.

In this case the opportunity of studying the circulation both when fluid was present in the pericardial cavity and after it had been removed was unusually favorable.

METHODS

All observations relating to the circulation were made in the morning while the patient was in a basal metabolic state. The cardiac output was measured by the acetylene method of Grollman.[10] The patient was trained beforehand to carry out her part in the procedure. On the morning of the measurement she reclined in a steamer chair for thirty minutes, during which time the radial pulse was counted at intervals of five minutes. At the end of one-half hour the acetylene-oxygen-air mixture was rebreathed. Three samples of gas were taken during each rebreathing period for estimation of the arteriovenous oxygen difference, as recommended by Grollman[10] and Grollman, Friedman, Clark and Harrison.[11] In order to be certain of obtaining a good mixture, the rebreathing was repeated twice at intervals of twelve minutes. If the arteriovenous oxygen differences calculated from the analysis of the first set of three samples agreed well with each other, indicating that mixing had been satisfactory, the other samples were not always analyzed. The arteriovenous oxygen differences recorded in Table I are the averages of those which were analyzed. Shortly afterward, the oxygen consumption was measured in a Benedict-Roth spirometer. The vital capacity, height, and weight were then recorded. The patient rested again, now lying down. In succession, allowing time between each two procedures for the patient to return to a basal metabolic state, the circulation time was measured, the venous pressure estimated, and the arterial pressure recorded.

In order to measure the arm-to-tongue circulation time, 5 c.c. of a 20 per cent solution of decholin[12] were injected rapidly (1 to 2 seconds) through an 18-gauge needle into an antecubital vein while the patient was lying quietly in the supine position. The needle was left in place and the test repeated one and a half to two minutes after the first measurement had been made. The time taken was that which

elapsed between the beginning of the injection and the perception of the bitter taste, and the figures recorded in Table I are averages of the two readings. The injection time, which ranged from 1 to 2 sec., was also recorded in the original protocols.

The venous pressure in a large antecubital vein was measured by the direct method,[13] with the arm on a level with the right auricle. The apparatus, consisting of an L-tube of glass, attached to a 3-way stopcock, a syringe, and 18-gauge needle, was filled with a solution of sterile normal saline. Normal pressure with this technique ranges from 4.0 to 9.0 cm. of saline. The antecubital vein of one arm was reserved for the injection of decholin, and that of the other arm for estimation of the venous pressure.

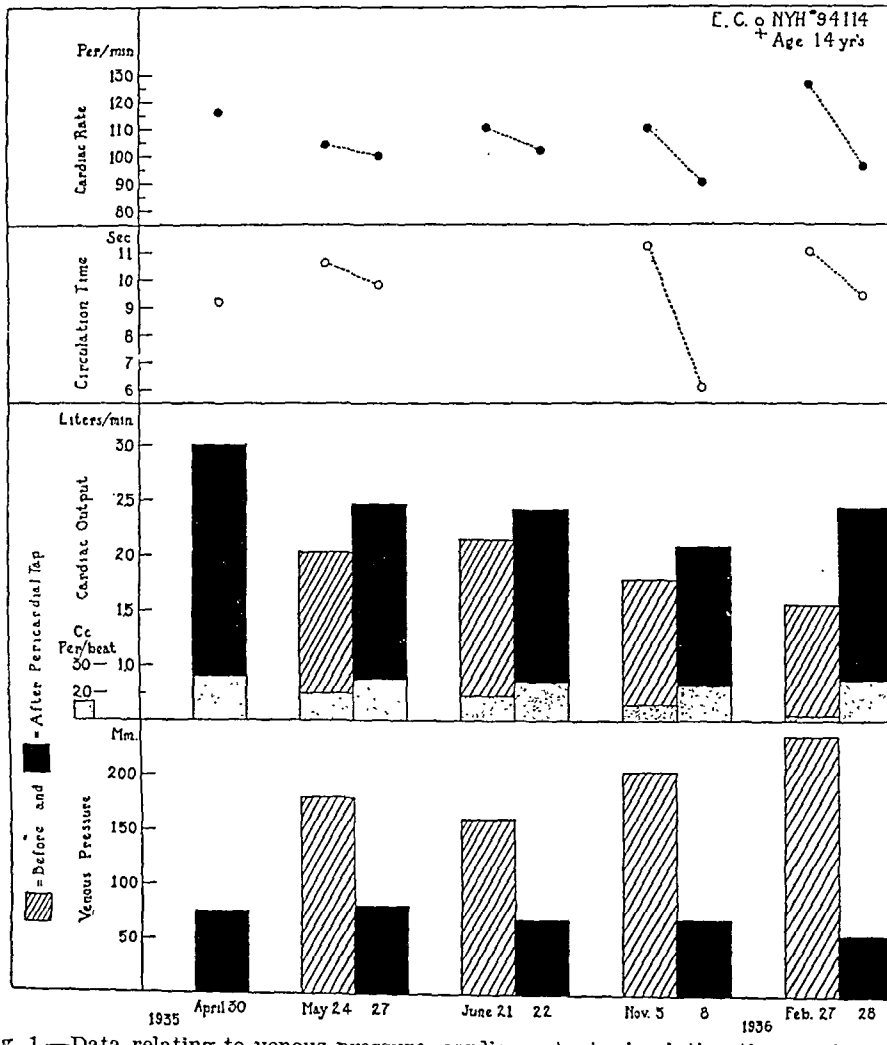

Fig. 1.—Data relating to venous pressure, cardiac output, circulation time, and cardiac rate in the presence of pericardial effusion before and after paracentesis.

OBSERVATIONS

Effect of Pericardial Effusion on Cardiac Output.—The cardiac output was measured on five occasions before and after tapping the pericardium. On April 30, 1935, six days after 1,100 c.c. (first tap) had been removed, the cardiac output measured 3.00 liters, equivalent to 3.00 liters per square meter per minute, and 26 c.c. per beat (Table I, Fig. 1). On May 24, 1935, when fluid had reaccumulated and the patient exhibited the signs and symptoms of cardiac tamponade, the cardiac output had

TABLE I

OBSERVATIONS RELATING TO THE CIRCULATION IN THE PRESENCE OF PERICARDIAL EFFUSION AND AFTER THE REMOVAL OF FLUID

DATE	HEIGHT CM.	WEIGHT KG.	BODY SURFACE AREA SQ. M.	TIME WITH REFERENCE TO TAP	AMOUNT PERICARDIAL FLUID REMOVED C.C.	OXYGEN CONSUMPTION C.C. PER MIN.	BASAL METABOLIC RATE (%)	ARTERIOVENOUS OXYGEN DIFFERENCE C.C.	CARDIAC OUTPUT L./MIN.	CARDIAC OUTPUT L./SQ. M./MIN.	CARDIAC OUTPUT C.C./BEAT	CARDIAC RATE PER MIN.	VITAL CAPACITY C.C.	VENOUS PRESSURE MM. SALINE	ARM-TO-TONGUE CIRCULATION TIME SEC.	INTRA-PERICARDIAL PRESSURE MM.	BLOOD PRESSURE MM. HG	NUMBER OF THE TAP	DATE OF PERICARDIAL TAP
1935 April 30	139.5	25.8	1.03	After	1100	143	+1	48.0	3.00	3.00	26	116	1300	74	9.2		96/68	1	Apr. 24
May 24	139.5	30.9	1.11	Before	600	149	-2	73.5	2.03	1.83	20	104	900	183	10.6		94/68	2	May 25
May 27	140.0	29.8	1.09	After		143	-5	58.2	2.46	2.26	25	100	1100	83	9.8		96/70		
June 21	140.5	31.4	1.13	Before	750	149	-1	69.7	2.14	1.90	19	110	950	159			96/64	3	June 21
June 22	140.2	30.6	1.11	After		141	-8	58.4	2.41	2.17	24	102	900	68			102/76		
Nov. 5	140.5	32.3	1.14	Before	500	145	-8	82.1	1.77	1.55	16	110	600	203	11.2	100-110	128/78	7	Nov. 5
Nov. 8	140.5	30.6	1.11	After		139	-9	66.9	2.07	1.90	23	90	1000	70	6.1		94/72		
Exploratory Operation November 15, 1935																			
1936 Feb. 27	141.0	31.8	1.13	Before	1175	147	-4	95.7	1.54	1.36	12	126	500	235	11.0	100	105/75	13	Feb. 27
Feb. 28	141.4	30.5	1.12	After		133	-14	55.0	2.42	2.20	25	96	800	55	9.4		102/75		

fallen to 2.03 liters per minute, which amounted to 1.83 liters per square meter per minute and 20 c.c. per beat. On May 25, 1935, 600 c.c. of fluid were removed (second tap), and forty-eight hours later the cardiac output had increased to 2.46 liters per minute, or 2.26 liters per square meter per minute and 25 c.c. per beat. Results similar to these were obtained on three other occasions (the third tap, June 21, 1935, the seventh, Nov. 5, 1935, the thirteenth, Feb. 7, 1936). In short, the cardiac output per minute and cardiac index and output per beat were decreased when fluid was present in the pericardial cavity and increased following its removal. Measurements made after surgical exploration of the heart were not significantly different from those recorded before operation (Table I, Fig. 1, Feb. 27, 1936).

Effect on Arteriovenous Oxygen Difference.—The arteriovenous oxygen difference was on each occasion greater when fluid was present in the pericardial cavity (Table I) than after tapping. Since there was no significant alteration in oxygen consumption per minute, the wide arteriovenous oxygen differences in the presence of tamponade were associated with low cardiac outputs, and the smaller ones with the greater outputs.

Effect on Venous Pressure.—The venous pressure was measured whenever the cardiac output was estimated, as well as on many other occasions. It rose as fluid accumulated in the pericardial cavity, varying between 159 and 235 mm. of saline (Table I, Fig. 1) at the time the cardiac output was diminished; it fell to normal levels (55 to 85 mm. of saline) after tapping, when the cardiac output had increased.

Effect on Circulation Time.—The arm-to-tongue circulation time varied between 10.6 and 11.2* seconds when pericardial effusion was present and decreased to a range of 6.1 to 9.8 seconds (Table I, Fig. 1) after each paracentesis. The longer circulation times were found when the cardiac output was decreased and the venous pressure elevated and the shorter ones after tapping, when the cardiac output was greater and the venous pressure normal (Table I, Fig. 1).

Effect on Cardiac Rate.—The heart rate was faster when the sac was distended with fluid than it was after tapping (Table I, Fig. 1). This was found to be the case each time, but the slowing was greater on some occasions than others. This variation probably depends on the amount of fluid which was present before tapping, and how much was removed.

Effect on Arterial Pressure.—The arterial pressure was low when the patient was in her best state, and, since paracentesis was at times followed by a slight rise and at other times by a slight fall, no conclusions can be drawn from this case (Table I).

Effect on Vital Capacity.—According to the Wilson and Edwards[15] standards, the vital capacity of this patient was approximately 50

*The average time for normal children from 8 to 16 years of age is 8.6 seconds, the range 5.0 to 13.5 seconds.[14]

per cent below average. On May 24, 1935, it measured 900 c.c. (Table I), and three days later, after removal of 600 c.c. of pericardial fluid, it measured 1,100 c.c. On all but one occasion the vital capacity was increased after removal of fluid. Part of the decrease in vital capacity when fluid was present was due to encroachment of the pericardial contents upon the space usually occupied by the lungs.

DISCUSSION

It is clear, therefore, that when fluid accumulated in the pericardial cavity in sufficient quantity to give a tamponade effect the venous pressure rose, the cardiac output became less and the output per beat smaller, the circulation time longer and the heart rate faster (Fig. 1).

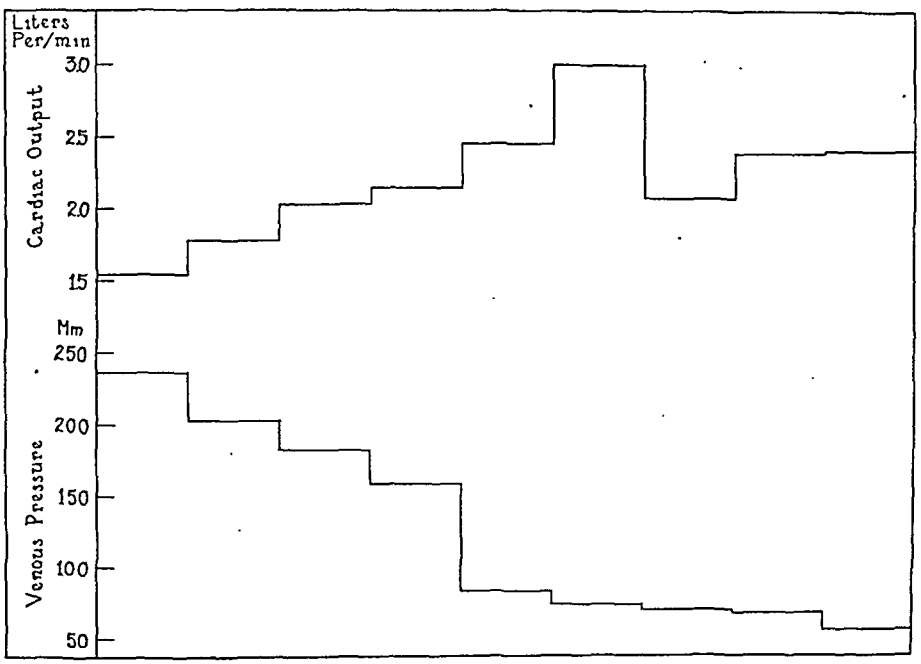

Fig. 2.—Data relating to venous pressure and cardiac output. The venous pressure measurements have been plotted in decreasing order, disregarding chronologic sequence, and the corresponding measurements of cardiac output have been plotted above (see text).

These results in a human being parallel Cohnheim's[9] original observations on animals. On removal of the fluid by mechanical means the venous pressure fell, the cardiac output increased per minute and per beat, the circulation time became shorter and the heart rate slower (Fig. 1). In short, there was a great decrease in the capacity of the heart as a pump when there was increase in fluid in the pericardial cavity. The filling of the heart was interfered with in proportion to the amount of fluid present, and the degree of interference was indicated by the rise in venous pressure. Diminution of the cardiac output per minute and per beat was due to decreased filling and probably also to the fact that the diastolic size of the heart was restricted.

There is a linear correlation between venous pressure and cardiac output in cardiac tamponade. In Fig. 2 the venous pressures have been

arranged in decreasing order, disregarding chronologic sequence, and above them the corresponding levels of cardiac output have been plotted. A steplike decrease in venous pressure is associated with a steplike rise in cardiac output. With high venous pressures the two curves are approximately mirror images of each other. At the higher levels of venous pressure (235 mm.) the cardiac output is greatly diminished (1.54 liters per minute), and, as the venous pressure falls the cardiac output increases in a surprisingly uniform fashion, this relationship being maintained until the venous pressure has fallen to 83 mm., the normal range,

A. *B.* *C.*

Fig. 3.—Infrared photographs which show the superficial veins. *A* was taken Oct. 30, 1936, fourteen days after a paracentesis, when the patient was comfortable. *B* was taken Nov. 16, 1936, when tapping needed to be done, and *C* was taken Nov. 21, 1936, after removal of 1000 c.c. of fluid from the pericardial cavity.

where fluctuations in cardiac output are observed. This relationship attains added significance through consideration of the fact that these observations were made over a period of many months and are plotted without chronologic sequence. The rise in venous pressure gives a measure of the decrease in cardiac output and the degree of tamponade.

The degree of distention of the superficial veins was studied by means of infrared photographs. The photograph taken Oct. 30, 1936 (14 days after the twenty-third tap, Fig. 3*A*), at a time when the patient was comfortable, showed moderate engorgement of the veins. A second photo-

graph, taken Nov. 16, 1936 (Fig. 3*B*), when the patient had developed evidence of cardiac tamponade and the venous pressure was elevated, showed that the superficial veins were somewhat more engorged and that a few more veins were visible. A third photograph, taken Nov. 21, 1936 (Fig. 3*C*), after removal of 1,000 c.c. of fluid (twenty-fourth tap), showed that the superficial veins were less prominent.

On two occasions (Feb. 27, 1936, and April 21, 1936) the pressure in the pericardial sac was measured and found to be 100 mm. and 75 mm. of the fluid, respectively. The effect of gradual removal of fluid on the venous pressure was also observed. On Feb. 27, 1936, the venous pressure fell sharply from 198 mm. to 155 mm. as soon as the needle was inserted into the pericardial cavity (Fig. 4), which means that the flow of fluid into the tapping system was sufficient to relieve tension

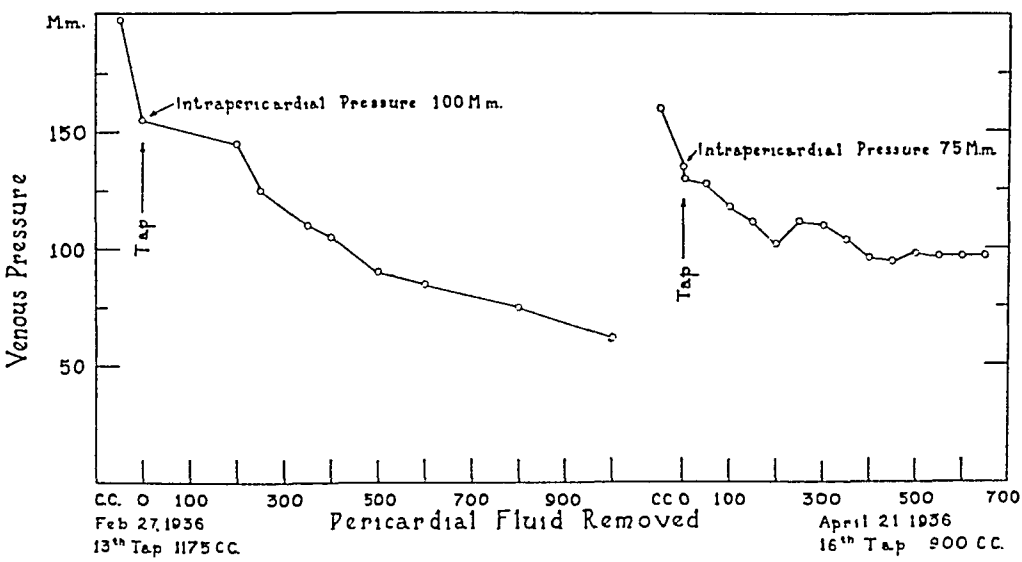

Fig. 4.—Changes in venous and intrapericardial pressure which occurred when successive amounts of pericardial fluid were removed.

in the sac. The venous pressure then fell rapidly with the removal of each 50 to 100 c.c., reaching 100 mm. when about 400 c.c. had been removed; thereafter its fall was more gradual. Results similar to these were observed on the second occasion (April 21, 1936).

Fineberg[1] has found that, in dogs an amount of salt solution equal to approximately one-third the weight of the heart can be injected into the pericardial cavity before interference with ventricular filling (estimated by rise in venous pressure) occurs. Assuming that the same is true of human beings, he estimates that 80 to 100 c.c. of pericardial fluid can be present before any rise in venous pressure occurs. From these observations it may be inferred that the pericardial sac affords ample space for dilatation of the normal heart. On the other hand, these experiments may be taken to indicate to what extent the volume of the heart may be reduced, rather than to demonstrate the distensibility of the sac.

SUMMARY

The accumulation of fluid in the pericardial cavity in man results in:

1. Marked decrease in the volume output of blood from the heart, both per minute and per beat.
2. Increase in the arm-to-tongue circulation time.
3. Rise in venous pressure.
4. Increase in intrapericardial pressure.
5. Increase in heart rate.
6. Decrease in vital capacity.

All of these abnormal conditions tend to disappear when excess pericardial fluid is removed.

It appears that:

1. Decrease in cardiac output is due for the most part to interference with the inflow of blood into the right heart; it cannot be said, however, that contraction is not also impaired.
2. Increase in the amount of pericardial fluid is associated with progressive decrease in cardiac output and rise in venous pressure.
3. Venous pressure falls rapidly at first, and then slowly, to a normal level as fluid is removed from the pericardial cavity.

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ABSORPTION FROM THE PERICARDIAL CAVITY IN MAN*

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IN ANOTHER paper[1] relating to changes in the circulation in the presence of massive pericardial effusion, attention was directed to our lack of information concerning the pericardium. Little is known about the mechanism of formation of pericardial fluid, of its absorption, and of the factors controlling its quantity under normal circumstances. Drinker and Field[2] have studied absorption from the pericardial cavity of rabbits. They concluded that the pericardium in this animal is a singularly inert protective membrane. Simple solutions did not permeate this thin membrane but were absorbed by the subepicardial blood capillaries. Serum and graphite particles were absorbed with extraordinary slowness. There was practically no lymphatic drainage; that which occurred was around the base of the heart and along the fat deposits in the pericardium. In short, the subepicardial lymphatics were entered with great difficulty from the pericardial sac.

We have been unable to find observations relating to absorption from the pericardial cavity in human beings. We have had the opportunity of making certain studies relating to this subject in a patient suffering from chronic recurrent pericardial effusion, and these observations form the subject of this paper.

E. C., history 94114, a white female, 14 years of age, exhibited chronic recurrent pericardial effusion of unknown etiology. Therapeutic pericardial taps for the relief of cardiac tamponade and the secondary consequences of the effusion were required at intervals of approximately four weeks. It was apparent that observations relating to the absorption of dyes from the pericardial cavity would give information about the size of the molecules which could find their way out of this cavity. We chose two nontoxic dyes in common use in the clinic, namely, phenolsulphonephthalein and vital red. The molecular size of the former is small, and of the latter, large. Accordingly, we performed experiments to discover, on the one hand, whether dyes placed in the cavity entered the blood stream and came out by way of the kidneys, and, on the other hand, whether dyes injected into the blood stream appeared in the pericardial cavity.

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Phenolsulphonephthalein.—After removal of as much pericardial fluid as possible (1200 c.c.) and while the needle was still in place, 2.0 c.c. of phenolsulphonephthalein were injected into the cavity on Jan. 18, 1936, on the occasion of the eleventh tap. Of this, 82.5 per cent was recovered in the urine within 24 hours (Table I). Two of the early specimens were lost, and the total amount excreted on this occasion is not known. When observations were made on a second occasion, Sept. 16, 1936 (twenty-second tap, 1,800 c.c.), 99 per cent of the dye was excreted by the kidneys in 37 hours, 23 minutes, and 85 per cent of it in the first 22 hours, 38 minutes (Table I). On still another occasion, Feb. 27,

TABLE I

URINARY EXCRETION OF PHENOLSULPHONEPHTHALEIN PLACED IN THE PERICARDIAL CAVITY AT THE CONCLUSION OF TAP

DATE	TIME	VOLUME OF URINE (C.C.)	PHENOLSULPHONE-PHTHALEIN EXCRETED IN URINE (PER CENT)	PHENOL-SULPHONE-PHTHALEIN PLACED IN PERICARDIAL CAVITY (C.C.)
1/18/36	2:10 P.M.			2.0
	3:00 P.M.	50	Lost	
	6:10 P.M.	50	7.5	
	8:00 P.M.	30	Lost	
	8:15 P.M.	45	12.5	
1/19/36	6:00 A.M.	100	40.0	
	8:35 A.M.	130	10.0	
	10:25 A.M.	150	7.5	
	2:00 P.M.	100	7.5	
	3:00 P.M.	250	5.0	
			82.5 (24 hours)	
9/16/36	10:22 P.M.			2.0
	10:30 P.M.	98	0.0	
9/17/36	9:10 A.M.	115	35.0	
	12:00 NOON	195	15.0	
	3:45 P.M.	210	18.0	
	6:30 P.M.	110	10.0	
	9:00 P.M.	70	6.0	
9/18/36	6:00 A.M.	100	10.0	
	11:45 A.M.	60	5.0	
			85.0 (22 hr. 38 min.)	
			99.0 (37 hr. 23 min.)	

1937, all of the dye was excreted within 15 hours. Absorption, therefore, rises slowly to a maximum so that the greater part of the dye is removed within twenty-four hours.

When this dye was given intravenously, however, it apparently did not find its way in the reverse direction, that is to say, into the pericardial cavity. On Nov. 19, 1936, at 1 P.M., 1.0 c.c. was given intrave-

nously. At 1:30 P.M., when the twenty-fourth pericardial tap was performed and 1,000 c.c. of fluid removed, dye could not be detected in it. The patient had, however, excreted all the dye in the urine at the end of four hours.

Vital Red.—On one occasion, June 2, 1936 (eighteenth tap, 650 c.c.), vital red, 1.0 c.c. of a 1.5 per cent solution for each 5 kg. (a total of 6.0 c.c.) was injected into the pericardial cavity at the conclusion of the tap. This is approximately the same amount as that used in the estimation of the circulating blood volume. When used for this purpose, it appears in the urine and imparts to it a bright red color which is readily detected. In these studies colorimetric titration was not made because the color of the urine made it difficult to match the standard. In this instance amounts detectable by the eye had not been excreted in the urine within 35 hours after injection. At the time of the next tap (the nineteenth), July 1, 1936, twenty-nine days later, the fluid which was removed was dark pink in color, indicating the presence of this dye. That it had not been absorbed was obvious. It may be stated that the usual color of the pericardial fluid was greenish yellow, and the presence of the dye on this occasion was easily detected. In short, a dye of the molecular size of vital red did not find its way readily out of the pericardial cavity.

On Feb. 6, 1936, 3.0 c.c. of 1.5 per cent vital red was given intravenously at 1:15 P.M. At 5:15 P.M. 1,150 c.c. of fluid were removed by pericardial tap (twelfth). Dye was not detected in the fluid on gross examination. This dye, therefore, as well as phenolsulphonephthalein, did not leave the blood stream to enter the pericardial cavity in the time allowed, which was four hours.

From these observations it is clear that the relatively small molecules of phenolsulphonephthalein were absorbed readily from the pericardial cavity, while the larger molecules of vital red were not absorbed, or at least to a negligible extent, and remained in the cavity. On the other hand, neither of the two dyes in the concentrations given had entered the pericardial cavity from the circulating blood at the end of four hours.

Our experiences with these dyes of different molecular sizes probably find their explanation in the observations made by Drinker and Field,[2] which have already been mentioned. The small molecular size of phenolsulphonephthalein permits it to enter the subepicardial capillaries. On the other hand, the large size of the vital red molecule no doubt places it in the same group as serum and graphite particles (Drinker and Field[2]). These studies confirm the observation of these investigators that entrance into the lymphatics from the pericardial cavity occurs apparently with the greatest difficulty and very slowly.

We have no data which allow us to state the nature of the defect which permits the formation of pericardial fluid in excessive quantities in this

patient, but certain of the chemical constituents of the fluid may account for or contribute to the failure of absorption. We refer particularly to its total protein content. On the occasion of the sixteenth tap, April 20, 1936, the total protein content of the pericardial fluid was 6.2 gm. per cent (albumin 2.5 gm. per cent, globulin 3.7 gm. per cent); the blood serum proteins had remained in the range of 6.0 gm. per cent to 6.5 gm. per cent (albumin 3.7 gm. per cent to 4.2 gm. per cent; globulin 2.2 gm. per cent to 2.9 gm. per cent). In short, since the total protein content as well as the albumin and globulin fractions of the fluid and of the blood were almost identical, the oncotic pressures of the two should be approximately the same; this being the case, there would be no opportunity for the passage of these substances from the pericardial cavity into the subepicardial blood vessels such as occurred in the case of the small molecule of phenolsulphonephthalein. Drinker and Field[2] have also demonstrated that serum leaves the pericardial cavity of rabbits with extraordinary slowness. This being the case, even though the protein content of the two systems—subepicardial capillaries and pericardial cavity—differed, absorption of fluid did not occur, a fact which the following chance observations demonstrated. On the occasion of the twenty-fourth tap, Nov. 19, 1936, the total protein content of the fluid was 4.2 gm. per cent (albumin, 1.2 gm. per cent; globulin, 2.6 gm. per cent) and the total serum protein 6.7 gm. per cent (albumin 2.9 gm. per cent; globulin 2.9 gm. per cent).

It may be that conclusions derived from the observations relating to this case are not true for the normal pericardium. It appears likely, however, that they are pertinent. In the first place, they yield data similar to those recorded by Drinker and Field. In the second place, although the heart was found covered with a small amount of organized fibrous exudate at the time of an exploratory operation, this did not hinder absorption of phenolsulphonephthalein by way of the subepicardial capillaries. The patient died of pneumonia on Nov. 27, 1937. Autopsy indicated that the pericardial lesion was the primary one, and that the clinical manifestations were a consequence of the accumulation of fluid in the pericardial sac. The diagnosis was chronic pericarditis. The pericardium was slightly thickened only, and its appearance did not differ significantly from that observed at the time of operation.

CONCLUSIONS

In the case which we have studied it was found that:

1. A dye of the molecular order of phenolsulphonephthalein entered the blood stream readily from the human pericardial cavity, presumably by way of the subepicardial capillaries.

2. On the other hand, larger molecules, such as those of vital red, were neither absorbed by way of these vessels nor to any appreciable extent by the lymphatics, since this dye was present in the fluid removed one month later.

3. These two dyes, when injected intravenously, did not appear in the pericardial fluid.

4. The pericardial fluid in this patient with respect to its total protein content and serum and globulin fractions was similar to blood serum; for this reason the fluid could not readily pass back through the subepicardial vessels into the blood stream, for the two systems (blood and pericardial fluid) were approximately in equilibrium so far as the oncotic pressure of the proteins was concerned.

Our observations yield data relating to the human pericardium which are in agreement with those already recorded by Drinker and Field with respect to the rabbit's pericardium.

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ANEURYSM OF THE HEART

The Clinical Recognition of Aneurysm of the Left Ventricle

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ANEURYSM of the heart is usually looked upon as a somewhat rare and unusual pathologic condition. Libman[1] in his post-mortem studies found that aneurysm of the left ventricle occurred fifteen times as often as Hodgkin's disease. White,[2] in a recent textbook on heart disease, says that "cardiac aneurysms . . . have been known to pathologists for centuries, and their connection with coronary disease recognized for many years, but in the practice of medicine these conditions have only in recent years been regarded as of much clinical significance and as possible to diagnose." He further states that "both cardiac aneurysm and rupture are as a rule only post-mortem findings, undiagnosed before the autopsy although they may have been suspected in a few cases." Even Lewis,[3] in his most recent book on disease of the heart, alludes only briefly to cardiac aneurysm. Steel,[4] as recently as 1934, believed that the signs of cardiac aneurysm are so indefinite that relatively few cases have been diagnosed clinically. Applebaum and Nicolson,[5] in an excellent pathologic study of occlusive disease of the coronary arteries, found fifty-seven cases of aneurysm of the heart out of one hundred fifty cases in the atherosclerotic group, an incidence of 38 per cent. Fifty-six of the fifty-seven aneurysms involved the left ventricle, and of these, forty-five were situated in parts of the left ventricle which should permit of clinical recognition.

It seems to the writer that aneurysm of the left ventricle can often present distinctive clinical manifestations and should be correctly diagnosed during life in many cases. It is for this reason that this subject is completely reviewed, and an illustrative case presented. It is also hoped that a better understanding of the pathology of coronary artery occlusion, myocardial infarction, and cardiac aneurysm will lead to an attempt to prevent aneurysm formation.

HISTORICAL

Cardiac aneurysms as we understand them today were unknown to Morgagni and Sénac. The first true observation was probably made by Galeati[6] in 1757, and this was followed two years later by a case report by Walter.[6] In 1784 Portal[6] accurately described a case in a

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sixty-five-year-old woman who died suddenly following a cold bath. She had a chronic cardiac aneurysm with a fesh rupture of the wall near the sac. In 1803 Vetter[6] wrote about "cardiac aneurysm where only a part of the ventricle, mostly the apex, appears expanded in the form of a sac." He differentiated this condition from ventricular dilatation. The reports of Kreysig[6] in 1815, Berard[6] in 1826, and Brett[6] in 1827 followed shortly thereafter. In 1815 Hodgson[6] published a case of rupture of the heart in which closure of the vessel leading to the ruptured area was demonstrated. He recognized that the closure was the cause of the local disease of the heart muscle. In 1827 Breschet[6] summarized the literature and collected all of the previously published cases. He failed, however, to appreciate the relationship between the coronary artery disease and the resultant cardiac aneurysm. He believed that aneurysms were caused by localized ulceration and an incomplete rupture of part of the myocardium with a consequent dilatation of the overlying heart muscle. His interest in the subject was aroused by the death of the tragedienne, Talma, who on post-mortem examination was found to have a cardiac aneurysm. About the same time Cruveilhier, Peacock, Caraigle, Faget, Mercier, and Thurman[7] recognized and described fibrous changes in the myocardium and believed that they were caused by local inflammatory processes.

In 1840 Rokitansky[6] added greatly to this subject when he described ninety-four cases of cardiac aneurysm, in seventy-two of which the left ventricle was involved. He believed that there was a connection between ossification and "impenetrability" of the coronaries on the one hand, and fatty metamorphosis and "partial outpocketing" of the cardiac wall on the other. He did not emphasize the pathogenetic relationship very strongly.

It was Mercier,[6] in 1857, who recognized the relationship between cardiac rupture and cardiac aneurysm, but he overlooked the diseased coronary arteries. Pelvet,[8] in 1867, noted that the coronary arteries were often altered and even obliterated, but he also did not think that they played a significant role in the pathologic changes. Virchow,[6] in 1868, mentioned disease of the coronaries in thirteen cases of cardiac aneurysm but regarded it as a secondary, unimportant finding.

It was not until 1880 to 1885 that the current conception of coronary artery closure and the pathogenesis of myocardial infarction, cicatrization, and resultant cardiac aneurysm were clearly presented. During this period Tautin, Lancereaux, Joseph Loeb, and Ziegler[6] contributed their important papers. They pointed out that coronary thrombosis was followed by areas of myocardial softening and, if the individual survived the acute stage, the softened area of the myocardium was replaced by scar tissue which later could develop into a cardiac aneurysm.

Ziegler was the first to use the term "myomalacia" of the heart; he stated that "occlusion of the coronaries produces cardiac anemia and softening, and subsequent dilatation results in its rupture." In 1881 Cohnheim and V. Schulthess-Rechberg[6] recognized that so-called chronic myocarditis and the frequent aneurysmatic dilatation which accompanies it were merely sequelae of a primary disease of the coronary arteries.

The next important advance of our knowledge in this field began with the work of Leyden[9] in 1884-1886 on sclerotic myocarditis. He studied the changes in the coronary arteries in order to determine their relationship to myocardial lesions, and he pointed out that slight narrowing of the coronaries could be responsible for the formation of a localized fibrosis of the myocardium which later could develop into an aneurysm. Odriozola, Nicholle, and Huchard[10] also made similar observations in France at about the same time. In 1887 Rendu[11] also emphasized the importance of changes in the coronary arteries in the formation of cardiac aneurysms.

Marie[6] in 1896, enlarging on Ziegler's viewpoint, re-emphasized the association of aneurysm of the heart and myocardial infarction with coronary artery disease. In a remarkable thesis which he wrote for his degree of Doctor of Medicine he developed the "myocardial theory of cardiac aneurysm" and stated that "a thrombus forms at the site of a narrow point of a coronary artery and the entire portion of myocardium degenerates. If rupture of the heart does not occur, the necrotic area becomes cicatricial and leaves in its place a fibrous sac. The aneurysm is thus formed of the above." He noted that the myocardial infarctions most often involved the anterior surface and apex of the left ventricle. In all of the cases of aneurysm which Marie and his co-workers presented before the anatomical societies in 1894 and 1895, obliteration of a coronary artery was always found. Fredet,[12] Rendu,[11] and Bureau[13] had previously described cases of aneurysm of the heart in which the coronary arteries were said to be normal. These cases, of course, did not fit in with the myocardial theory of Marie, and, in order to explain the apparent discrepancy, Marie hypothesized embolism of a coronary artery with subsequent dislodgment of the clot. He noted, however, the extreme rarity of coronary embolism, and believed that the aneurysms in these cases might have been due to other changes in the myocardium; furthermore, he emphasized the possibility that most aneurysms were, without doubt, associated with obliteration of a branch of a coronary artery. There have been few additions to our knowledge of this subject since the time of Marie. At the end of his thesis he discusses the symptomatology of aneurysm. In a few cases there were certain clinical features which he believed were helpful in making a diagnosis. One which he stressed particularly was the gallop rhythm first mentioned by Rendu.

Marie attempted to differentiate it from the gallop rhythm associated with renal disease. He pointed out the fact that the gallop rhythm of aneurysm of the heart was heard best, not at the apex, but above the apex, and was transmitted towards the ensiform cartilage. The clinical manifestations of cardiac aneurysm were not well recognized during that period.

The work of Sternberg[14] (1914) on "chronic partial aneurysm of the heart" consisted of a careful review of all the previous publications dealing with cardiac aneurysm, together with many interesting observations and comments of his own. He believed that syphilis was the etiologic factor in most of the cases of coronary artery disease and stressed the importance of intensive antisyphilitic treatment as a means of preventing cardiac aneurysm. In the light of our present knowledge it is clear that syphilis plays a very minor role in the causation of coronary thrombosis.

Pletnew,[15] in 1926, reviewed three hundred reported cases of cardiac aneurysm and stated that only six had been diagnosed intra vitam. He added the seventh and eighth correctly diagnosed cases.

Morris,[16] in 1927, reviewed the subject of cardiac aneurysm and added five cases found at autopsy. In none was cardiac aneurysm suspected ante mortem. In speaking of aneurysms of the heart, he stated "they are, for the most part, beyond the reach of treatment and are rarely recognized during life."

Even in 1928, Medlar and Middleton[17] stated that "the ante-mortem recognition of cardiac aneurysm is unusual," while Sutton and Lueth[18] as recently as 1931 stated that the diagnosis of this condition is usually impossible. They pointed out that an irregular outline found on percussion or with the aid of the roentgenogram may lead one to suspect its presence.

Most of the recent literature on cardiac aneurysms deals either with post-mortem statistics or roentgenologic findings. Steel[4] states that "the signs of cardiac aneurysm are so indefinite that relatively few cases have been recognized clinically." He believes that a careful fluoroscopic examination in the various degrees of rotation is most essential for the roentgenologic diagnosis. There are, in addition, a few reports of cases diagnosed during life by means of roentgenograms, in which the diagnosis was confirmed on post-mortem examination.[19-23] Shookhoff and Douglas[24] reported a case in which the condition was recognized by means of roentgenologic examination. Fogel[25] also described a case of aneurysm of the left ventricle in a man who at the time of writing was still able to do a little work.

PATHOLOGY AND METHOD OF FORMATION OF CARDIAC ANEURYSMS

It is well recognized that a myocardial aneurysm is caused by a lack of nutrition of a part of the heart muscle which usually develops after

occlusion of a coronary artery. Inasmuch as the left anterior descending coronary artery is most frequently involved, an aneurysm usually occurs in the anterior wall of the left ventricle near the apex. The relationship of the left ventricle to the chest wall makes possible the clinical recognition of an aneurysm. The aneurysm occasionally found on the posterior wall of the left ventricle is usually due to occlusion of the right coronary artery, and as yet has not been recognized clinically. The aneurysm begins to form during the period of acute myomalacia. Experimental observations on animals illustrate clearly the formation of a localized bulging in the heart wall.[26] When the anterior descending branch of the left coronary artery is experimentally tied off in the dog, that portion of the ventricular wall which loses its blood supply assumes a dark color and is seen to bulge outwards with each cardiac systole.

It may be assumed that the same thing takes place in the human heart during the early period of an acute coronary artery thrombosis, especially if the area of infarction has been extensive. This constitutes the first stage in the formation of a cardiac aneurysm. If the individual survives the acute attack and recovers, healing of the infarcted area is accomplished by replacement fibrosis. This area remains the weakest part of the ventricular wall, and, as intraventricular pressure rises with each contraction of the ventricle, the weakest part gradually "gives" and dilates. Finally, an aneurysm of a portion of the ventricular wall is formed at the site of the previous myocardial infarction. The aneurysm may consist of a very small bulge or may actually form a sac as large as the ventricle itself.

The experiments of Sutton and Davis,[27] who studied the effect of exercise on experimental cardiac infarction in dogs, throw considerable light on the formation of cardiac aneurysms, and indicate how they may be prevented in man. After a preliminary training period on a motor-driven treadmill, five dogs were operated upon and the ramus descendens anterior of the left coronary artery was ligated 1 to 2 cm. from its origin. One dog was given a six-day postoperative rest period, two dogs a two-day rest period, and the remaining two dogs a three-day rest period, before exercise was resumed. Exercise was then continued for periods varying between 70 and 390 days, when each animal was autopsied. It was found that the heart of the dog which was rested for six days had a small, firm, well-contracted scar without thinning of the ventricular wall. In the other dogs, exercise within three days after the production of myocardial infarction resulted in thin scars with definite aneurysmal bulging in each instance.

If there has been a pre-existing hypertension with an increased intraventricular pressure, as in the case to be described, then an added factor in forming the aneurysm is present. The walls of these aneurysms are often very thin and translucent, which accounts for the fact

that they may rupture very easily. The endocardial surface of the aneurysm is often the seat of mural thrombi from which fragments can break off and be carried to any part of the general circulation.

CLINICAL MANIFESTATIONS

The clinical description by Aran[28] was probably the earliest and closest to our present concept and was based upon diagnostic points gleaned from autopsy findings. He emphasized the importance of the presence of "a considerable enlargement of cardiac dullness and diffuse and increased cardiac beat, contrasting with weakness of the pulse." Kasem-Beck[6] added further that a marked elevation of intercostal spaces together with a small pulse is "a certain symptom of left ventricular aneurysm."

Since 1926, Libman[29-32] has frequently called attention to the two most important physical signs associated with aneurysm of the left ventricle, namely, the presence of a pulsation more marked between the apex and the sternum than at the apex proper, and a poor, dull, first heart sound.

In summation one may say that a clinical diagnosis of aneurysm of the left ventricle may be made when the following history and signs are present:

1. History of a preceding attack of coronary artery occlusion.
2. Visible and palpable apical pulsation, well inside the left outer border of cardiac dullness.
3. A dull first heart sound, of poor tone, with little or no muscular quality.

The subject is best summed up by saying that what one sees is out of all proportion to what is heard. After seeing and feeling a vigorous precordial pulsation, one expects to hear a loud, booming first heart sound, as in a case of hypertension; instead, a dull, almost inaudible first heart sound is heard. These signs are of greater importance when found in an individual who has no hypertension and whose heart is only slightly or moderately enlarged.

Fig. 1 illustrates in a schematic fashion the position of the maximal visible and palpable pulsation of the cardiac apex in relationship to the left outer border of cardiac dullness in (a) the normal heart, (b) the hypertensive heart with hypertrophy of the left ventricle, and (c) the heart with an aneurysm of the left ventricle.

Furthermore, there may be found, although less frequently, the following:

1. A visible and palpable heaving, double, precordial pulsation.
2. A localized systolic murmur inside the apex.
3. Gallop rhythm.

The gallop rhythm is the least constant auscultatory finding, and, when present, it is best heard, as was originally mentioned by Rendu,[11]

nearer the ensiform process than the cardiac apex. Libman pointed out that the gallop rhythm is often best heard in the recumbent position. It has been my experience that the gallop rhythm when associated with cardiac aneurysm is usually heard during the stage of circulatory failure and that its disappearance is associated with the return of compensation. This probably explains its inconstancy, as is demonstrated in the case herein described. In addition, there may be definite roentgenographic evidence of aneurysm of the left ventricle. If this is present, then the triad of (1) antecedent coronary artery occlusion, (2) clinical recognition, and (3) roentgenologic proof, is complete, and the diagnosis certain.

The following case is of unusual interest because this triad was complete, and aneurysm of the left ventricle was recognized clinically. The patient, after having suffered a coronary artery occlusion with a resulting aneurysm of the left ventricle, lived for five and one-half years, and was able to work without marked evidence of cardiac or circulatory failure.

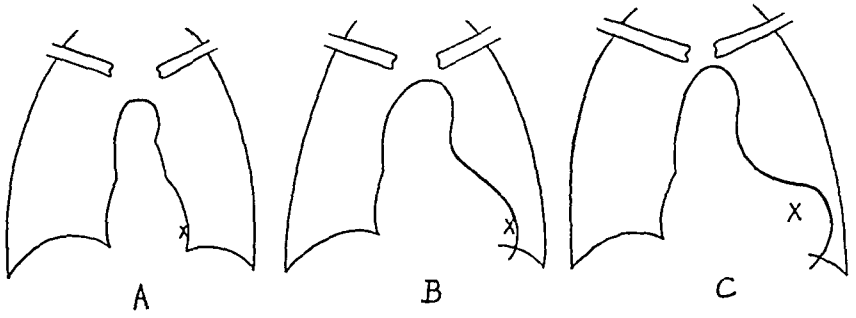

Fig. 1.—Schematic illustration portraying the maximal visible and palpable apical impulse *X* in relationship to the left outer border of cardiac dullness in *A*, the normal heart, *B*, the hypertensive heart with hypertrophy of the left ventricle, and *C*, the heart with an aneurysm of the left ventricle.

CASE REPORT

S. B. (B. I. H. 44972), male, aged 55 years, entered the Beth Israel Hospital Nov. 24, 1931, and gave the following history: Four years before, he had consulted his family physician because of some mild pressure in the upper chest. He was told he had high blood pressure and was given some "powders." His symptoms disappeared, and he felt perfectly well until the onset of the present illness. About six weeks before admission he began to experience pressure over the upper sternum, and difficulty in breathing, occurring mainly after eating and not related to exertion. With some regulation of the diet, the symptoms abated. Two and a half weeks before admission to the hospital he was suddenly seized with a severe attack of pressing pain across the chest, and he became very short of breath. He was then put to bed and given a "hypodermic." The pressure and shortness of breath disappeared in about two days, he felt perfectly well, and remained in bed only part of the day. Three days before admission, he was seized with dyspnea and severe precordial pain radiating down the left arm. He continued to have such attacks frequently and was in pain upon admission to the hospital.

Physical examination upon admission was as follows: The patient was a middle-aged adult male complaining of pain in the left chest and some shortness of breath.

He appeared anxious and was slightly cyanotic and moderately orthopneic. Pressure over the styloid process (Libman test) elicited no response, indicating that he was markedly hyposensitive to pain stimuli. Both pupils were contracted (morphine). The heart was markedly enlarged to the left; percussion showed that the left border was at the anterior axillary line. A double heaving apical pulsation was visible and palpable about 2.5 cm. inside the outer border of cardiac dullness. The rhythm was normal and the rate was 80 per minute. The first sound at the apex was dull and distant; gallop rhythm and a faint pericardial rub were heard. The sounds at the base were practically inaudible. Moist râles were heard over the bases of

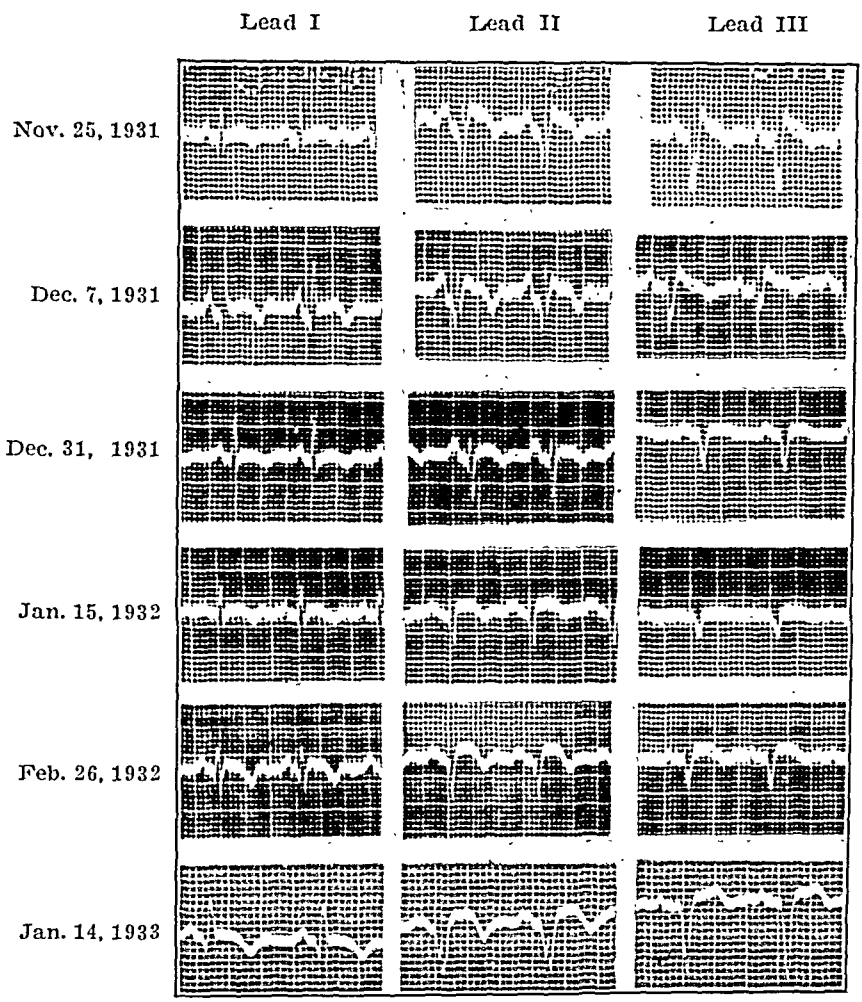

Fig. 2.—Serial electrocardiograms taken during the patient's hospital stay and one and one-half years later (last line) showing typical type T_1 changes indicating damage to the anterior and apical portion of the left ventricle.

both lungs and the liver was felt two fingerbreadths below the costal margin. The temperature on admission was 101.6° F.; the blood pressure was 130/98; and the leucocytes, 76 per cent of which were polynuclears, numbered 10,100 per cubic millimeter. The sedimentation time was 78 mm. per cent in 45 minutes. The blood Wassermann reaction was negative, and blood chemistry figures, normal. The urine was negative except for a trace of albumin.

Because of the history suggesting acute coronary artery occlusion, the pericardial rub, and the presence of a marked double precordial pulsation over the apex which could be seen and felt well inside the left outer border of cardiac dullness, together with a dull first sound, the diagnosis on admission was aneurysm of the apex of the

left ventricle following coronary thrombosis and myomalacia cordis in an individual with a pre-existing arterial hypertension. The patient remained in the hospital, confined to bed for ninety-nine days. The first electrocardiogram (top row, Fig. 2), taken on admission, revealed definite evidence of recent myocardial damage. Serial electrocardiograms (Fig. 2), taken at intervals during the entire hospital stay, show progressive type T_1 changes; the T-waves became deeply inverted in Leads I and II, and then tended to return toward normal. During the first four weeks, the patient was very ill. The temperature ranged between 101° and 103° F., there were frequent attacks of precordial pain requiring large doses of morphine, and he had many attacks of vomiting so that for several days fluids had to be given by rectum and hypodermoclysis. The sedimentation rate never dropped below 21 mm. per cent in 45 minutes (normal 6 to 10), and a persistent leucocytosis was present. The temperature became normal on the sixty-ninth day and remained normal for one week; it then rose again and continued to be slightly elevated until the eighty-second day, after which there was no fever at any time. About two and one-half months after admission, the patient was well enough to be transported to the x-ray department for a teleoroentgenogram (Fig. 3), which was interpreted by Dr. I.

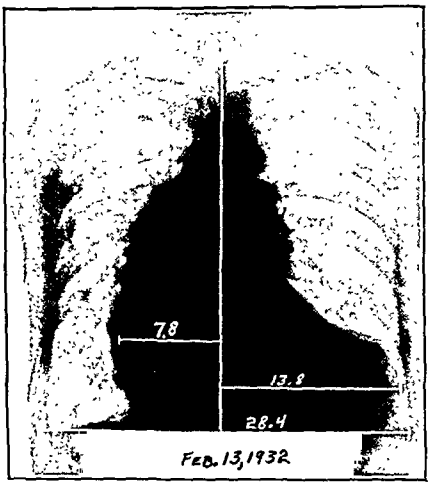

Fig. 3.

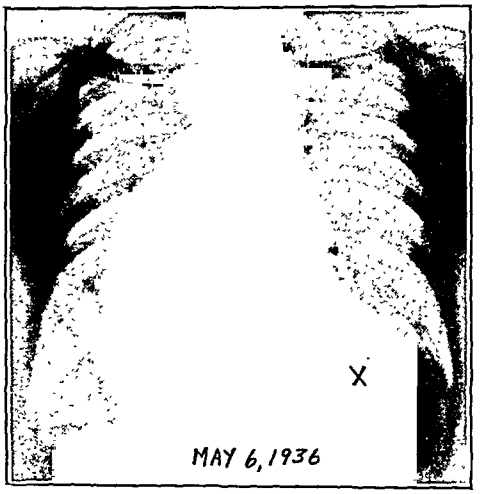

Fig. 4.

Fig. 3.—Teleoroentgenogram taken two and one-half months after the attack of coronary artery occlusion showing a marked bulge of the outer portion of the left ventricle (aneurysm). A definite indentation is seen where the arrow is pointing.

Fig. 4.—Teleoroentgenogram taken May 6, 1936, showing essentially the same cardiac contour as seen four years before (Fig. 3.). The mark *X* was obtained on the roentgenogram by fixing a lead marker *X* to the visible and palpable apical impulse on the chest wall.

Seth Hirsch as follows: "The heart shadow is abnormal in that there is a marked enlargement to the left due to left ventricular hypertrophy and dilatation. The outermost portion of the left ventricle protrudes above the level of the ventricular curve, suggesting the possibility of an aneurysm or dilatation. There is a marked diffuse dilatation of the aortic arch." The gallop rhythm heard on admission gradually disappeared, and the heaving of the precordium became more marked. The patient requested that he be allowed to leave the hospital and was sent home in an ambulance ninety-nine days after admission. Nothing more was heard from him until Jan. 14, 1933, about ten months later, when he answered a request to attend the follow-up clinic. He stated that he had remained in bed for eight weeks after leaving the hospital, entirely symptom-free, and then gradually increased his activities. He had been working four or five hours a day, standing up most of the time, cutting clothing patterns. He climbed about four flights of stairs daily and

had few complaints. He said, "I have never felt better in all my life." Physical examination at this time revealed almost the same cardiac findings as were present when he was discharged from the hospital. A heaving, double pulsation was visible over the lower precordium. The apex was best seen and felt 12.5 cm from the midsternal line in the sixth intercostal space, and percussion showed that the left border was 15 cm. from the midsternal line in the same interspace. The first sound at the apex was very distant and muffled, and the second aortic sound was only moderately accentuated. The rhythm was normal and the rate was 84 per minute. The blood pressure was 180/130. Both lungs were clear, and the liver and spleen could not be felt. There was no edema of the lower extremities. The teleoroentgenogram (Fig. 4) revealed a cardiac outline similar to that seen eleven months before, i. e., that of aneurysm of the apex of the left ventricle.* On fluoroscopy the heart

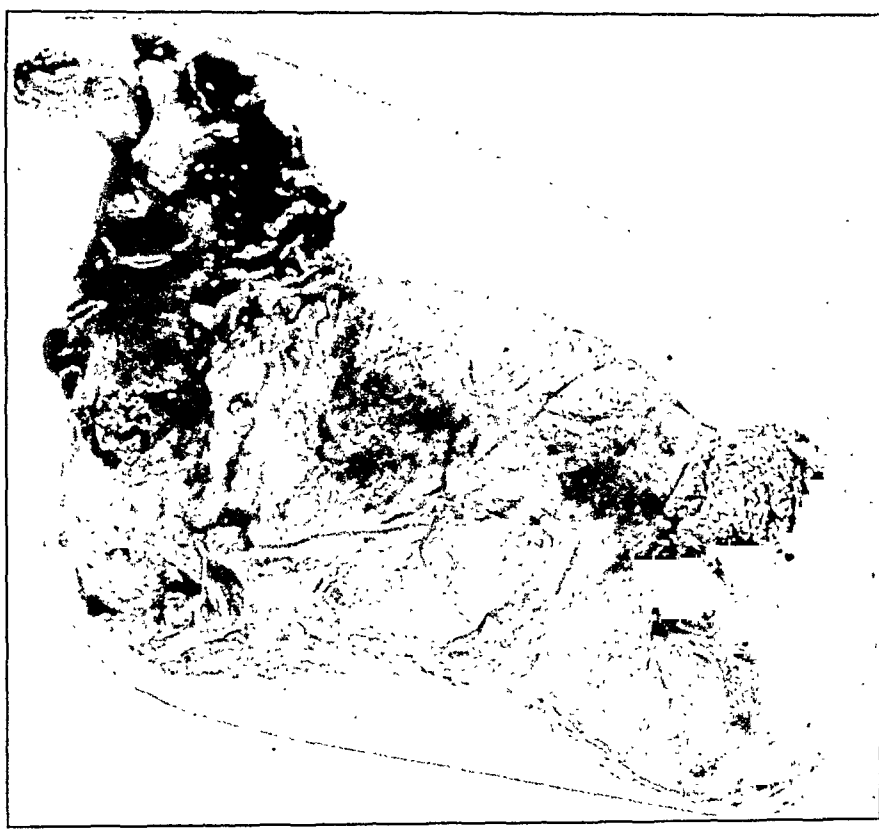

Fig. 5.—Photograph of the heart showing the approximate position it occupied in the chest.

was seen to be boot-shaped, occupying a transverse position. The apex of the left ventricle, which was lying practically against the left lateral chest wall, was rounded and totally immobile. The only portion of the left ventricular curve that was seen to move with each cardiac cycle was the straight portion just above the rounded apex (Fig. 4). The entire cardiac shadow shifted when the position of the patient was changed, indicating that the heart was not fixed by adhesions. Both leaves of the diaphragm moved freely. The electrocardiogram (last line, Fig. 2) showed left axis deviation with slight widening and notching of the QRS complexes. The T-waves in Lead I were still deeply inverted and had a cove-plane shape. The S-T intervals in

*It is suggested that in taking a roentgenogram of the heart in cases in which an aneurysm of the left ventricle is suspected, a lead marker (X) be placed over the clinical site of maximal apical pulsation (Fig. 4). This will illustrate graphically that the point of maximal apical pulsation is well within the left outer border of cardiac dullness.

Leads II and III were elevated and the T-waves angular. The serial electrocardiographic changes in this case were of the T_1 type, indicating infarction of the anterior and apical portion of the left ventricle, which is usually supplied by the left coronary artery. Barnes,[33] in his most recent study, always found infarction of the myocardium as previously predicted according to type T_1 or T_3 electrocardiographic changes. The patient continued to work and showed signs of increasingly diminished cardiac reserve until May 18, 1937, when he suddenly suffered an attack of nocturnal dyspnea, was found to have pulmonary edema, and, despite all therapeutic measures, died thirty-six hours later.

The autopsy, which was done by Dr. Alfred Plaut, was limited to the heart (Figs. 5 and 6). The heart measured 20 by 11 by 9 cm. The large vessels formed an angle of about 135° with the axis of the heart proper. The heart was irregularly

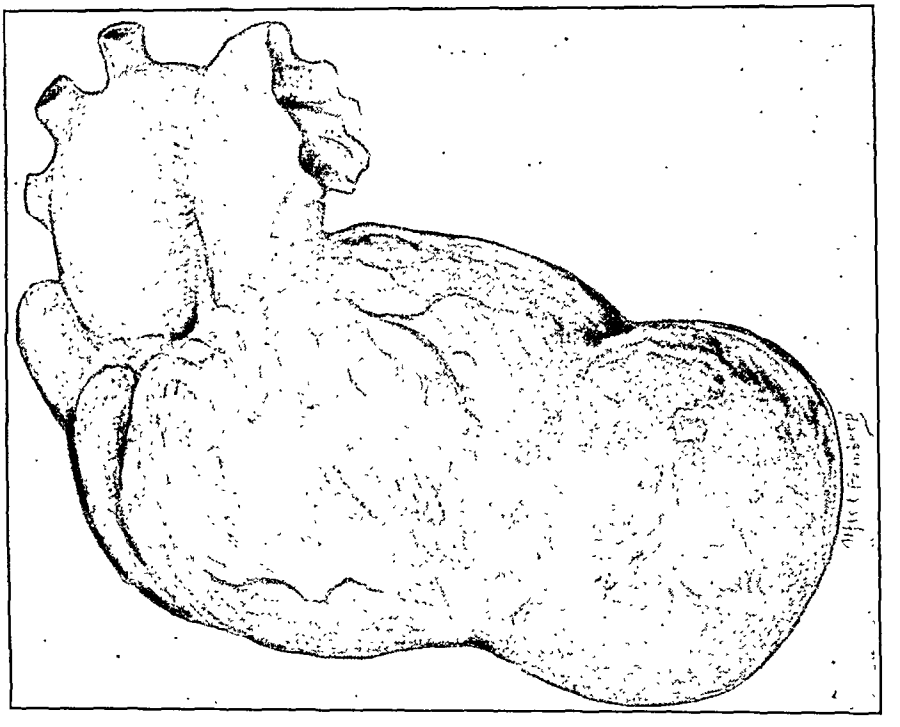

Fig. 6.—Drawing of the heart showing the well-defined indentation between the aneurysm and the remainder of the left ventricle.

sausage-shaped, having one maximum of thickness slightly above the middle, and another slightly above the lower pole. There was no apex, the lowermost portion being formed by a firm, rather regularly ovoid mass which had a transverse diameter of 11 cm., a depth of 10 cm., and a length of about 9 cm. from the lower pole to the groove which separated it from the remainder. The diaphragm was adherent at several points and the phrenic nerves were seen in their downward course. The pericardium was densely adherent over the round swollen portion which took the place of the apex, and seemed to be very thin in this area anteriorly as well as posteriorly.

Above the groove which separated the aneurysm from the remainder of the heart the pericardial tissue could be shifted over the underlying myocardium but could not be lifted from it. These adhesions made it difficult to examine the coronary vessels from outside. Since the heart, as mentioned, was sausage-shaped, no edges could be made out. Its left side was entirely round.

The pulmonary conus was not distinct. The pulmonary ostium was 8 cm. wide; the tricuspid ostium, 15 cm. The pulmonary valves and their commissures appeared perfectly normal; the valves are slightly fenestrated; their bases are not fibrotic. The tricuspid valve also was normal. The right ventricle was narrowed by the thickened and bulging septum. In relation to the size of the whole heart the right

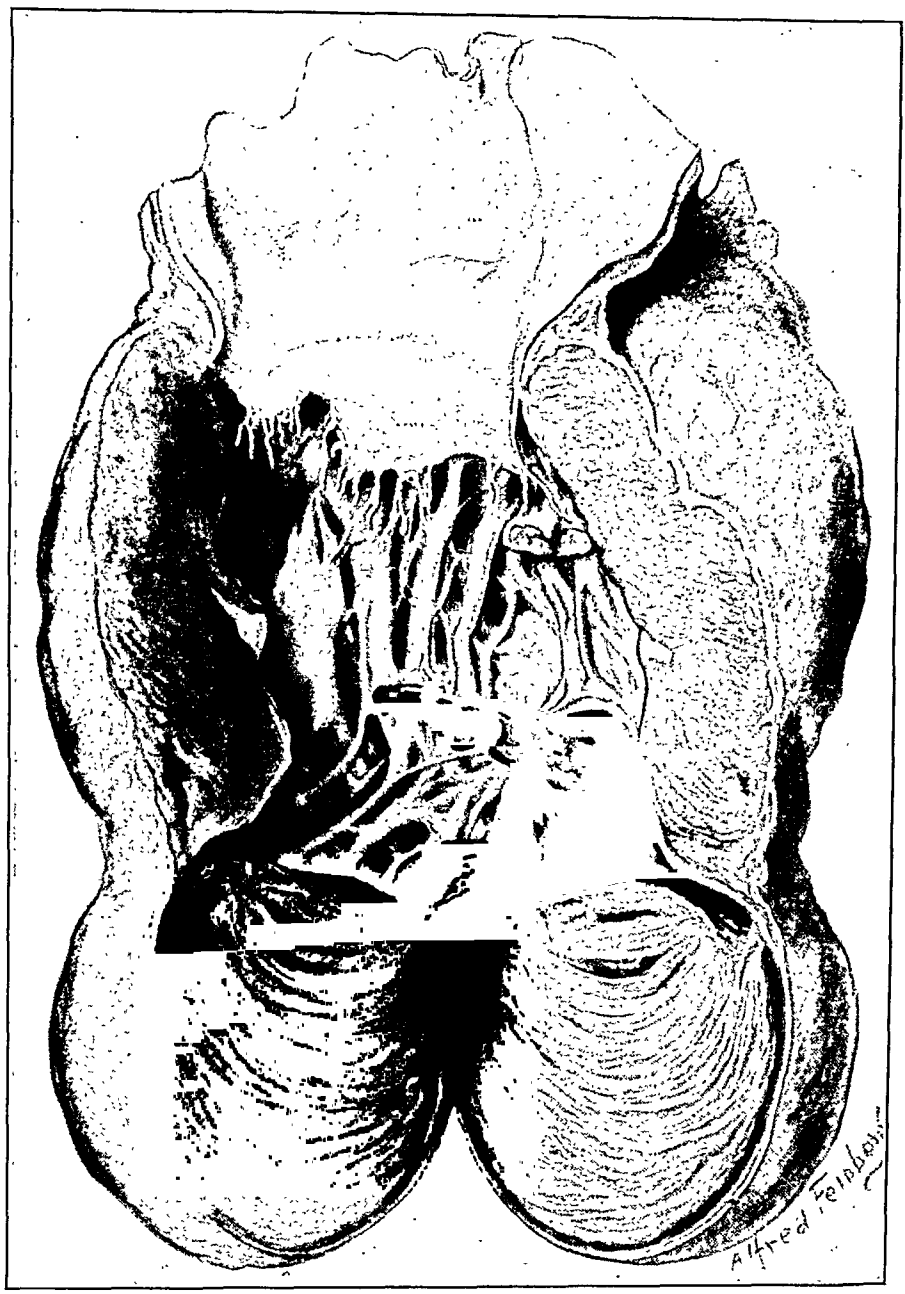

Fig. 7.—Drawing of the opened heart showing the wall of the aneurysm to be a thin-walled sac filled with a laminated blood clot with a mural thrombus attached to its ventricular surface.

ventricle was very small; its lowermost corner was situated 10 cm. above the groove which marked the upper edge of the lowermost portion of the heart. The anterior wall of the right ventricle, 4 cm. below the pulmonic ring, had a thickness of 7 mm.; it was slightly thicker further down. The papillary muscles and trabeculae appeared normal, slightly thin. The myocardium of the right ventricle was of a dull, pale

brownish color (so-called clay appearance). The pulmonary artery for 4 cm. above the ring had a smooth intima, beyond which a few small yellow plaques were seen, the firmest one corresponding to the scar of the ductus arteriosus. The yellow plaques extended into the ramifications of first order.

The right auricle appeared wide in relation to the small right ventricle, but not wide in relation to the size of the whole heart. The vena cava was 5.5 cm. wide; its inside was slightly yellowish. Both auricular appendages were small and did not contain thrombi. The opening of the coronary sinus was normal in width. In its neighborhood about six unusually large and distinct openings of Thebesian veins were noted. It may be added here that such openings are unusually distinct in the left auricle and ventricle also.

The mitral ostium easily admitted two fingers. The left auricle was slightly wider than the right and had complicated folds and ridges at the septum. The foramen ovale was closed by a very thin membrane. The fossa was narrow. There was a very distinct network of slightly protruding, fine, grayish-yellow lines in the endocardium on the left side. The mitral valve was normal, not vascularized, and its edges were not thickened. The left ventricle in its free portion was irregularly conical. The wall of the left ventricle, 4 cm. below the mitral ring, had a thickness of 2.3 cm. without trabeculae. Halfway between the atrioventricular groove and the apex of the heart the thickness was 3 cm.

The lowermost portion of the heart which, as mentioned, was separated by a shallow transverse groove, represented an aneurysm which was entirely filled with a laminated, firm, reddish-brown blood clot (Fig. 7). This clot was a multilayered mass, the layers being mostly parallel to the outline of the heart in the lower portion, but becoming more and more horizontal in the upper portion. Near the apex a smaller group of layers formed a more irregular system by itself. At the upper edge of this aneurysm the thickness of the ventricular wall suddenly tapered down to about 3 mm. Its thickness was approximately uniform at the whole periphery of the aneurysm. An exact judgment about the thickness was impossible on account of a thin, soft, dark-red layer which formed a kind of lining to the wall and could not be separated from it. Continuous with this layer above the multilayered firm clot, some soft, cruorlike material protruded into the lumen of the ventricle. The distance between the upper edge of the aneurysm and the base of the aortic valves was 10.5 cm. The upper portion of the left ventricle was wide, and its trabeculae and papillary muscles were very thick and round, comprising between them a system of deep grooves.

The color of the myocardium was as described in the right ventricle, with a little more yellow. The endocardium was not thickened except for the area directly below the aortic valves. The aortic ring was 8 cm. wide (the mitral ring could not be measured exactly). The aortic valves were thin, somewhat fibrotic at the base; the commissures were very slightly dissociated. The intima of the sinuses of Valsalva was diffusely yellow, and there were many yellow plaques in the ascending aorta, the arch, and the adjoining portions of the large neck vessels. No scars were seen in most of the heart muscle above the aneurysm. There was, however, an irregularly shaped gray area anteriorly to the left, directly below the mitral ring; it extended downwards about 2 cm.

As mentioned above, the coronary arteries were surrounded by the dense pericardial adhesions. The right coronary artery, after opening, had a width of 1.8 cm. It gave off two branches to the anterior wall of the right ventricle. One was 5 mm. wide at its mouth; 7 cm. further down this vessel had a width of 4 mm. The other branch was 3 mm. wide. There were two right posterior descending branches in normal position and with normal ramification.

The mouth of the left coronary artery was 10 mm. wide; 5 cm. further the width of the vessel was 7 mm. The left coronary artery sent four branches to the wall

of the left ventricle. An almost occluded branch farthest to the left probably represented the original circumflex artery. Of the two other branches, the larger one, which ran downward and slightly to the right, was occluded 2.5 cm. from its mouth for a distance of 1 cm. It then continued with a normal lumen and with a width of 4 mm. down to the edge of the aneurysm; it could not be traced further. This vessel originated 5 cm. from the mouth of the left coronary artery and was 7 mm. wide. The other branch ran straight downward; it was sclerotic but not occluded.

Two and a half centimeters from the mouth of the left coronary artery a thin-walled branch, 4 mm. in diameter, came out. It ran obliquely downward into the septum nearer the surface of the right ventricle. At the same point a branch 7 mm. wide came off, running downward and to the left. After a course of 1.5 cm. it divided into two branches also, spreading over the anterior wall of the left ventricle. Both, however, were considerably narrowed by yellow plaques.

The capacity of this coronary arterial system seemed very low in relation to the large bulk of the heart.

MICROSCOPIC EXAMINATION

In the myocardial wall at the upper end of the aneurysm only scant remnants of muscle tissue were seen, some of them with bizarre giant nuclei. The remainder of the tissue was hyaline fibrous tissue with irregular distribution of elastic structures.

Sections from both auricles and ventricles showed nothing unusual except for slight fibrosis. No changes in the medium and small vessels were found.

There was a little more diffuse fibrosis in the pulmonary artery.

The changes in the ascending aorta were characteristic of atherosclerosis. In addition, there were a few small foci of inflammation in the media and some accumulations of lymphocytes in the adventitia. Small arterial branches in the adventitia had intimal thickenings. There was nothing suggestive of syphilis.

SUMMARY AND CONCLUSIONS

The development of aneurysm of the heart has been reviewed from the clinical and pathologic viewpoints, and it has been pointed out that what was considered a great rarity and a unique diagnostic feat should in many instances be recognized.

One of the most important clinical features of this condition is the presence of a definite pulsation between the apex of the heart and the sternum, instead of at the apex proper. The case reported illustrates this fact very well, and it is further elucidated by a schematic illustration and roentgenograms. The reason for this secondary peculiar pulsation is explained by the anatomical position of the aneurysm itself.

The localization of an aneurysm of the left ventricle is possible roentgenographically if a bulge or an abnormal configuration of the left border of the heart can be demonstrated. The roentgenograms in this case (Figs. 3 and 4) show extremely well the thinning out of the aneurysmal portion of the ventricle. Special kymographic studies may be helpful in doubtful cases in which the roentgenographic silhouette does not show a definite bulge. In two such cases observed in which cardiac aneurysm was suspected clinically, the roent-

genogram merely showed a slightly enlarged heart without any definite bulge. Kymographic studies, however, revealed an aortic type of pulsation along the outer border of the left ventricle. In other words, with each systolic contraction of the left ventricle there occurred an outward bulge of the aneurysmal portion of the left ventricle.

Although it is significant and important to recognize an aneurysm of the heart, it is of far greater practical value to attempt to prevent this disabling condition. The case presented is extremely exceptional from this standpoint. If an aneurysm of the heart forms during the period of myocardial softening, the heart should be relieved of all excess work during this period, and this, of course, can only be accomplished by complete rest. This is especially true in cases of hypertension. It has been my experience that congestive heart failure develops rather quickly in individuals who have suffered a coronary artery occlusion and have developed an aneurysm of the left ventricle, and it makes the prognosis much more grave. The usual story the patient gives is that following an acute coronary artery occlusion *he was kept in bed a few days or one week and was then allowed up and around and went back to work; in about six to eight weeks he began to complain of shortness of breath on effort, and nocturnal dyspnea frequently followed.* On physical examination the patient is found to have congestive heart failure, and death often rapidly ensues. The lesson is that we must try to prevent the formation of a cardiac aneurysm in a patient who has suffered an acute coronary artery occlusion. In the light of our present knowledge this can best be accomplished by keeping the patient in bed at complete rest for at least six to eight weeks, with careful restriction of activities, both physical and emotional, for some time thereafter. Willius[34] has shown that complete healing of a myocardial infarct following a coronary artery occlusion does not occur until three to four months have elapsed.

It is hoped that this review of the literature, report of a case, and presentation of a definite diagnostic triad will aid in the clinical recognition of aneurysm of the heart and help to prevent it or some of its sequelae.

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ELECTROCARDIOGRAPHIC FINDINGS IN FORTY-FOUR CASES OF TRICHINOSIS*

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THE purpose of this paper is to present the electrocardiographic findings in forty-four patients with trichinosis in the second and ninth weeks of their illness. All of these patients were apparently healthy young adults, seventeen to twenty years of age. They had recently passed physical examinations, at which time no evidence of cardiac disease had been found. Details of the epidemic will be found in a paper now in preparation by Col. T. L. Ferenbaugh.[1]

One hundred eighty members of a Civilian Conservation Corps camp were considered as possibly exposed to the larvae by the ingestion of infested pork. Sixty-four of the above gave positive skin and precipitin tests. Forty-four were sufficiently ill to be placed in the hospital, and it was on this group that the electrocardiographic studies were made. Careful investigation established October 27 as the probable date of exposure. The first patient entered the hospital on November 9, and the last admission was on November 23. The electrocardiographic tracings were made on November 25 and January 10. These patients were carefully controlled and thoroughly studied. In order to determine the degree of infestation, five quantitative biopsies were done with the following results:

Patient No. 1	wt. 66.6 kg.	800 larvae per gram
Patient No. 37	wt. 61.4 kg.	33 larvae per gram
Patient No. 41	wt. 80.9 kg.	8 larvae per gram
Patient No. 43	wt. 68.4 kg.	22 larvae per gram
Patient No. 44	wt. 64.8 kg.	50 larvae per gram

Patient No. 1 suffered the most severe attack, as is indicated by the biopsy. Probably the biopsies in the other four patients would more nearly represent the average of the group studied.

In 1860 Zenker[2] reported the presence of trichinae larvae in the myocardium of a patient in whom the disease was fatal. Cohnheim,[3] who described the myocardial lesion in 1865, referred to it as "parenchymatous degeneration." From the work of more recent investigators[4] we now know the process is one of active cellular proliferation in the myocardium, with localized areas of necrosis and hemorrhage scattered throughout the heart muscle. There has been some difference of opinion as to the exact etiology of the myocarditis. Dunlap and Weller[5] con-

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TABLE I

NO.	ECG	PULSE	P-R INTERVAL	QRS INTERVAL	T-WAVE	COMMENT
1.	1st	70	0.12	0.06	up	
	2nd	65	0.12	0.06	Diphasic III	
2.	1st	75	0.16	0.06	Inverted III	
	2nd	100	0.16	0.06	Inverted III	
3.	1st	90	0.16	0.04	up	
	2nd	75	0.16	0.04	up	
4.	1st	80	0.16	0.06	up	Nodal premature beats
	2nd	90	0.20	0.06	up	
5.	1st	65	0.16	0.04	up	Slurred S-T II and III
	2nd	65	0.16	0.06	up	Slurred S-T II and III
6.	1st	75	0.16	0.04	Inv. III	Splintered II and III
	2nd	75	0.12	0.04	Inv. III	
7.	1st	80	0.18	0.08	Inv. III	Splintered I and II
	2nd	70	0.16	0.08	Inv. III	Splintered I and II
8.	1st	70	0.20	0.04	Diph. III	
	2nd	70	0.20	0.06	Diph. III	
9.	1st	75	0.14	0.06	up	Splintered II and III
	2nd	50	0.14	0.06	up	Splintered III
10.	1st	80	0.18	0.04	Diph. III	
	2nd	95	0.18	0.04	up	
11.	1st	95	0.18	0.04	Diph. III	
	2nd	75	0.16	0.06	Diph. III	
12.	1st	70	0.16	0.04	up	Splintered all leads
	2nd	85	0.16	0.06	Diph. III	Splintered II and III
13.	1st	70	0.16	0.04	up	
	2nd	80	0.16	0.06	Diph. III	
14.	1st	100	0.16	0.04	up	
	2nd	90	0.16	0.04	up	
15.	1st	80	0.20	0.04	Inv. III	
	2nd	80	0.16	0.04	Inv. III	
16.	1st	85	0.16	0.04	up	
	2nd	75	0.16	0.04	up	
17.	1st	65	0.16	0.06	up	
	2nd	70	0.16	0.06	Diph. III	
18.	1st	75	0.16	0.04	Diph. III	
	2nd	65	0.16	0.04	Diph. III	
19.	1st	55	0.20	0.04	Inv. III	
	2nd	55	0.20	0.04	Inv. III	
20.	1st	80	0.18	0.06	Inv. III	
	2nd	85	0.18	0.06	Inv. III	
21.	1st	70	0.16	0.04	Inv. III	
	2nd	80	0.20	0.06	Inv. III	

TABLE I—CONT'D

NO.	ECG	PULSE	P-R INTERVAL	QRS INTERVAL	T-WAVE	COMMENT
22.	1st	60	0.20	0.06	up	
	2nd	80	0.18	0.04	up	
23.	1st	50	0.18	0.06	Diph. III	
	2nd		0.18	0.06	up	
24.	1st	80	0.20	0.04	up	
	2nd	65	0.18	0.04	up	
25.	1st	90	0.14	0.04	up	
	2nd	90	0.14	0.04	up	
26.	1st	75	0.16	0.06	Inv. III	Splintered I and III
	2nd	80	0.16	0.06	Inv. III	
27.	1st	110	0.18	0.08	Diph. III	
	2nd	90	0.16	0.08	Diph. III	
28.	1st	70	0.16	0.04	Inv. III	
	2nd	75	0.16	0.04	Inv. III	
29.	1st	80	0.14	0.06	up	
	2nd	80	0.14	0.06	up	
30.	1st	65	0.18	0.06	up	
	2nd	70	0.18	0.06	up	
31.	1st	70	0.12	0.06	Inv. III	Splintered I and III
	2nd	80	0.12	0.06	Inv. III	Splintered I and III
32.	1st	100	0.20	0.06	up	
	2nd	90	0.20	0.06	up	
33.	1st	70	0.16	0.04	up	
	2nd	70	0.16	0.04	up	
34.	1st	90	0.14	0.06	Inv. III	
	2nd	85	0.14	0.06	Inv. III	
35.	1st	90	0.16	0.06	Inv. III	
	2nd	75	0.16	0.06	up	
36.	1st	75	0.24	0.06	up	
	2nd	75	0.20	0.06	up	
37.	1st	60	0.18	0.06	up	
	2nd	110	0.16	0.06	up	
38.	1st	70	0.20	0.08	up	
	2nd	70	0.18	0.08	Inv. III	
39.	1st	80	0.16	0.04	Inv. III	
	2nd	75	0.16	0.04	Inv. III	
40.	1st	80	0.16	0.06	Inv. III	
	2nd	70	0.16	0.06	Inv. III	
41.	1st	75	0.14	0.06	up	
	2nd	75	0.12	0.04	Inv. III	
42.	1st	80	0.16	0.08	up	
	2nd	95	0.16	0.08	up	
43.	1st	80	0.16	0.06	up	
	2nd	80	0.16	0.06	up	
44.	1st	70	0.16	0.04	Inv. III	
	2nd	80	0.16	0.04	Inv. III	

clude "that it is the presence of the larvae in the myocardium and their active migration and not a blood-borne toxic substance which produces the characteristic myocarditis." Zoller,[6] working with guinea pigs, noted that the larvae were rarely found after the second week. He believed they were either destroyed or left the myocardium through the blood stream. He concluded from his work that the myocardial lesion was only temporary, with no permanent residual damage.

The determination of myocardial damage by means of the electrocardiograph is becoming more and more satisfactory, but the interpretation of electrocardiograms is still subject to individual differences of opinion. Spink,[7] in an excellent review of eighteen cases of trichinosis, found six which showed electrocardiographic changes. These changes included an initial flattening or inversion of the T-wave, especially in

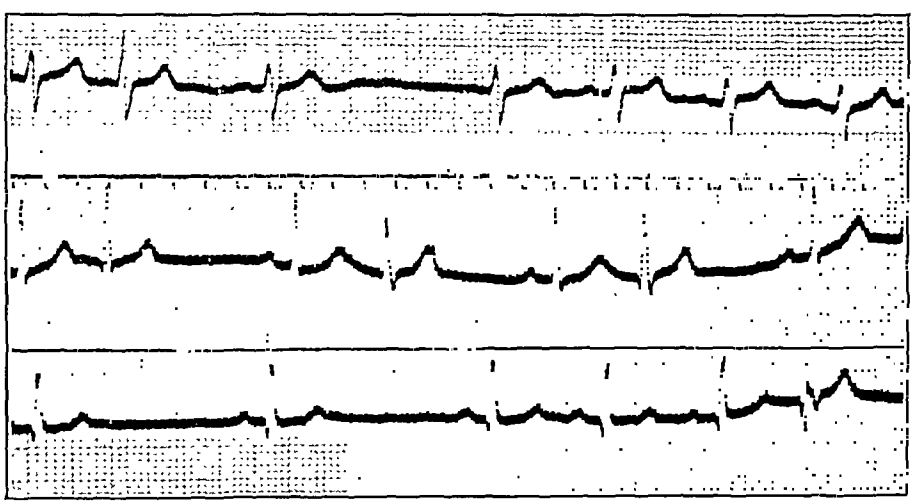

Fig. 1.—Case 4. Electrocardiogram taken November 25th: The irregularity is due to nodal premature contractions. In Lead II the premature contractions alternate with normal beats.

Lead II, the wave later becoming upright. He also noted low amplitude of the QRS complex and intraventricular block. Pardee[8] states that T-wave changes occur in this disease. Cushing[9] has presented a case of trichinosis showing this change very clearly.

The electrocardiographic findings in our cases are listed in Table I.

In none of the tracings were there definite changes in the T-wave in Lead II, nor were the amplitudes of the QRS waves abnormally low. In Case 4 the first electrocardiogram showed frequent premature contractions of the nodal type. There was no history of cardiac irregularity before this illness, and on the patient's discharge from the hospital the pulse was again regular, as indicated by the second electrocardiogram. In Case 36, the P-R interval was above normal limits in the first tracing, but had returned to normal limits on the second examination. In this case splintering was noted on the first tracing in Leads II and III, and was not found on the second examination.

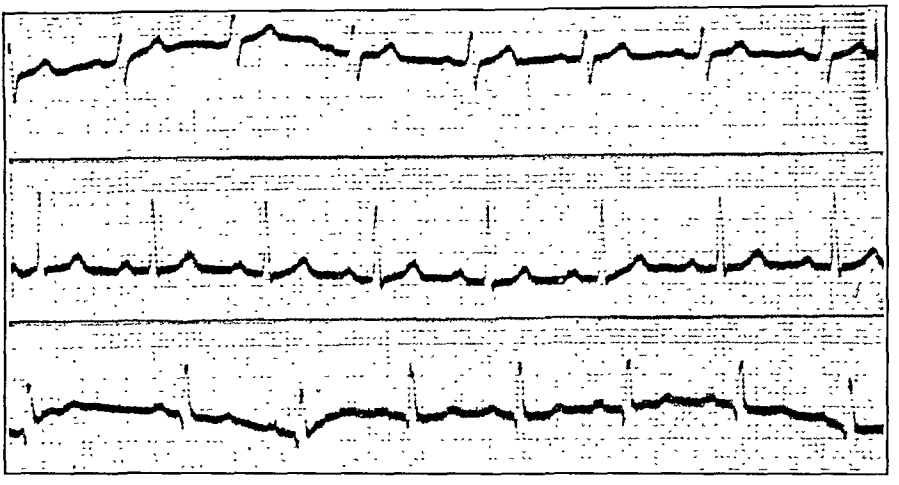

Fig. 2.—Case 4. Electrocardiogram taken January 10. There is no evidence of the previous irregularity.

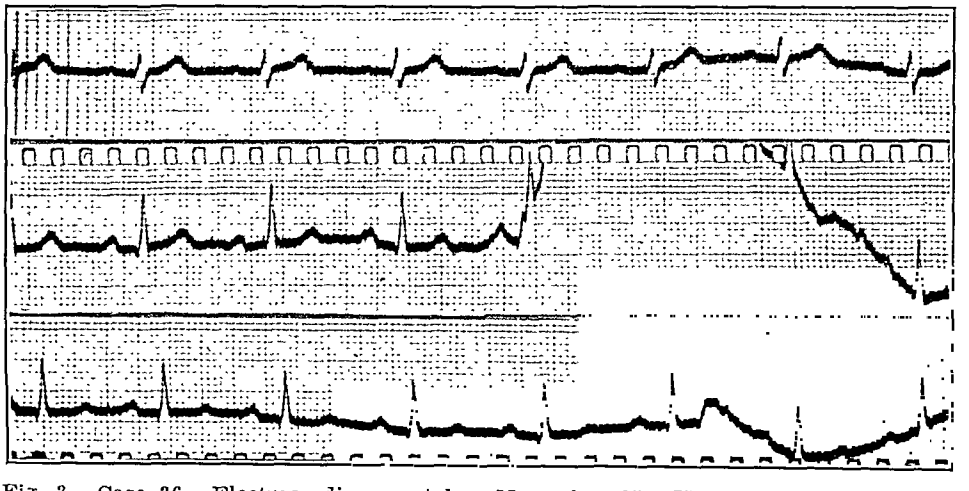

Fig. 3.—Case 36. Electrocardiogram taken November 25. The P-R interval is 0.24 sec.

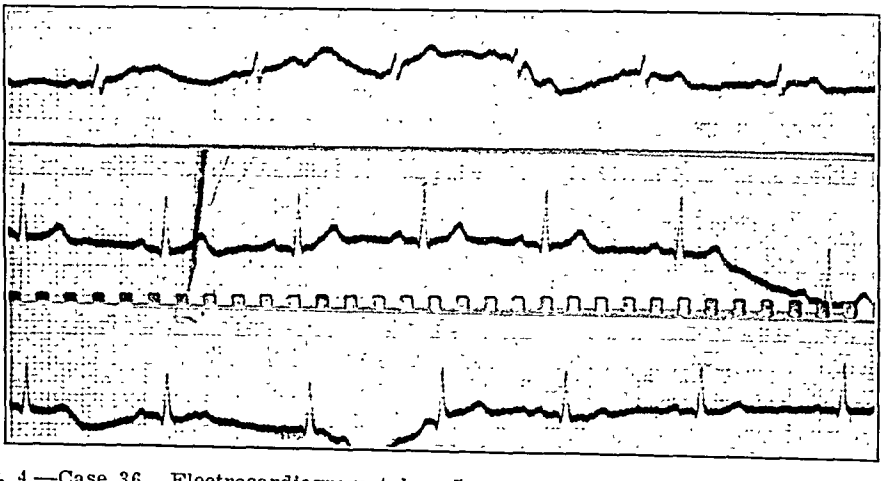

Fig. 4.—Case 36. Electrocardiogram taken January 10. The P-R interval is 0.2 sec.

SUMMARY

In forty-four cases of trichinosis of a mild type, two patients showed evidence of myocardial involvement. One found clinically to have coupled beats was proved to have nodal premature contractions which occasionally alternated with normal beats. The second patient showed a prolongation of the P-R interval.

The incidence of cardiac lesions demonstrable by clinical and electrocardiographic examination in this epidemic was 4.5 per cent, the damage apparently being only temporary.

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CARDIAC SYNCOPE DUE TO PAROXYSMS OF VENTRICULAR FLUTTER, FIBRILLATION, AND ASYSTOLE IN A PATIENT WITH VARYING DEGREES OF A-V BLOCK AND INTRAVENTRICULAR BLOCK

Report of Case*†

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IT HAS been recognized recently by numerous investigators,[1-8] particularly Schwartz and Jezer,[9] that ventricular fibrillation may occur as a transient disorder from which the patient recovers. Schwartz[1] and Schwartz and Jezer[9] have discovered the presence of phenomena between attacks which can be identified as prefibrillatory ventricular rhythms. In their patients these consisted of premature ventricular systoles from multiple foci which occurred with great frequency and were grouped in pairs and short runs. Most of these patients were suffering from advanced coronary sclerosis, and heart block in some form was not uncommon. The number of cases which have been described is still so small that it seemed to us worth while to report another which we have recently encountered. Several hundred feet of electrocardiographic tracings were obtained on this patient during her stay in the hospital. This included a record made during an entire period of syncope initiated by transient ventricular fibrillation and followed by recovery. Examination of the electrocardiograms of this patient and of those from similar cases in our files shows that the disturbance is due primarily to the activity of multiple ectopic pacemakers, impulse retardation and block.

CASE REPORT

E. K., a white woman, aged 59 years, was admitted to the Michael Reese Hospital on Dr. Sidney Portis's service July 30, 1937, because of frequent attacks of fainting. She had a previous history of long-standing hypertension and had been followed in the outpatient clinic for a number of years (with the exception of the year prior to admission).

Ten days before admission she developed dyspnea on exertion, cough, and generalized weakness. Five days before entrance she went to bed because of a severe dull headache and drowsiness. Before entering the hospital, she fainted several times.

On admission the patient appeared acutely ill. She had severe dyspnea and moderate cyanosis and was semiconscious. Examination of the lungs revealed dullness

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and increased fremitus over both bases and the right upper lobe posteriorly, and many crepitant râles. The heart was enlarged to the left, and the heart sounds were distant. The heart rate was 36 per minute with no pulse deficit, and there were occasional runs of rapid beating. The blood pressure was 260/90. The liver was enlarged. There were some venous varicosities in both lower extremities and moderate edema of the ankles. The rectal temperature was 101° F. There was no nitrogen retention, the urine was normal, and the blood counts were within normal limits.

The patient was placed in an oxygen tent and given ⅙ grain of morphine sulfate hypodermically. Her condition remained the same throughout the first day. She became more restless and refused her meals on the second day. An electrocardiogram (Fig. 2) which was obtained on this day revealed partial A-V block in addition to the intraventricular block she had shown in a record taken six years previously (Fig. 1). Barium chloride medication was begun on this day, and she received 3 grains in ½ grain doses over a period of two days. On the evening of the third day she became extremely restless. Her breathing became rapid and shallow, cyanosis increased, and a syncopal attack ensued. Her pulse at this time was rapid and very irregular; Cheyne-Stokes respirations appeared. Shortly thereafter she stopped breathing; there was no discernible pulse or heart tone, and the patient appeared lifeless. Within three minutes the pulse again became perceptible, and the patient began to breathe. A few convulsive twitchings and involuntary defecation and urination occurred at this time. The patient became extremely restless, almost violent, cried out in pain, and pointed to her legs and abdomen. An electrocardiogram (Fig. 3) was obtained immediately after this attack.

During the next few days she had five similar attacks, some of them of shorter duration. Quinidine sulfate in doses of 3 grains three times a day was given by mouth for five days, but this medication was ineffective because of continuous nausea and vomiting. Daily hypodermoclyses of 5 per cent glucose in saline were given. On the seventh day she was removed from the oxygen tent. The syncopal attacks became more frequent and continued to increase in number until her death. Electrocardiograms were obtained at frequent intervals, and examples of the chaotic rhythm are shown in Fig. 4 and Fig. 5. On August 10 a complete record during a syncopal attack with recovery was obtained (Fig. 6). This attack lasted three minutes, and her recovery was identical with that which had followed previous attacks, but within a few moments she again lapsed into coma. She had two more seizures during the night. The next morning her heart was so irregular that it was deemed advisable to administer quinidine intravenously.[10, 11, 12] A solution was made of 45 grains in 500 c.c. of normal saline (approximately 1 grain per 10 c.c. of isotonic saline solution) and a slow infusion was begun. After 9 grains had been given over a period of one and one-half hours, the patient became restless, developed another syncopal seizure which was similar to the others, and expired. Epinephrine injected directly into the heart and artificial respiration were without avail. Death occurred twelve days after admission to the hospital and approximately one month after her first syncopal attack. The patient had about twenty attacks of syncope during her hospital stay, the duration of the longest being three minutes.

The post-mortem examination was limited to the heart. Dr. O. Saphir, of the Department of Pathology, reported moderate narrowing in one of the branches of the left circumflex coronary artery due to an atherosclerotic plaque. No occlusions were found in the coronary arteries, and no gross evidence of myocardial infarction was apparent. Microscopic sections of the basal portion of the ventricular septum revealed some fibrous tissue which interrupted the conduction fibers. Moderate fibrosis was present throughout the heart.

COMMENT

Fig. 1 is a reproduction of the standard three-lead electrocardiogram taken June 29, 1931. It shows sinus rhythm, a rate of 91, normal A-V conduction (P-R interval, 0.18 sec.) and the common type of bundle branch block.

Fig. 2 shows the electrocardiogram taken July 31, 1937, one day after the patient's admission to the hospital. The intraventricular block persists; the sinus rate is 76, and 2:1 A-V block is now present in the limb leads. In Lead IV* the two strips mounted one beneath the other are continuous; the A-V block is greater than 2:1, and there is escape of the A-V node (beats marked E). The nodal escape caused interference dissociation and led to a 5:1 block in the last two instances. The bizarre appearance of the beat following the first nodal escape is apparently due

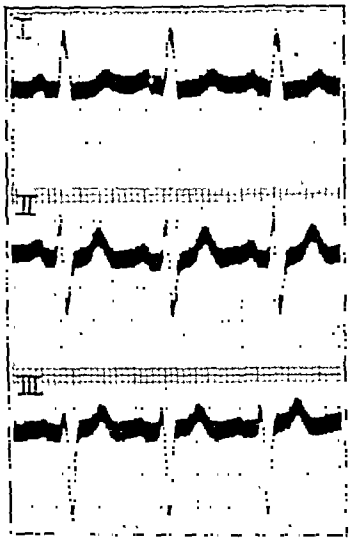

Fig. 1.

to abnormal spread through the ventricles. The same thing occurs to a lesser extent in the ventricular beat following the third nodal escape. Close examination of the record will reveal that the P-R intervals of the conducted beats fall into two categories, viz., 0.34 sec. ± .02 sec., and 0.15 ± 0.02 sec. (Table I). This unusual steplike variation in the P-R interval has, as far as we know, never been reported and has not been seen in any other record in our files. It suggests that there may have been two alternative paths through the A-V node and common bundle which joined before the bundle branches were reached.

Fig. 3 is a part of a three-lead electrocardiogram taken Aug. 1, 1937, which shows advanced partial A-V block. At times there is 2:1 A-V block, viz., at the beginning of Leads I and II, and at other times only

*In this and subsequent figures Lead IV refers to our old Lead IV. In terms of the Special Committee Report of the American Heart Association this is the inverted mirror image of CF_3.

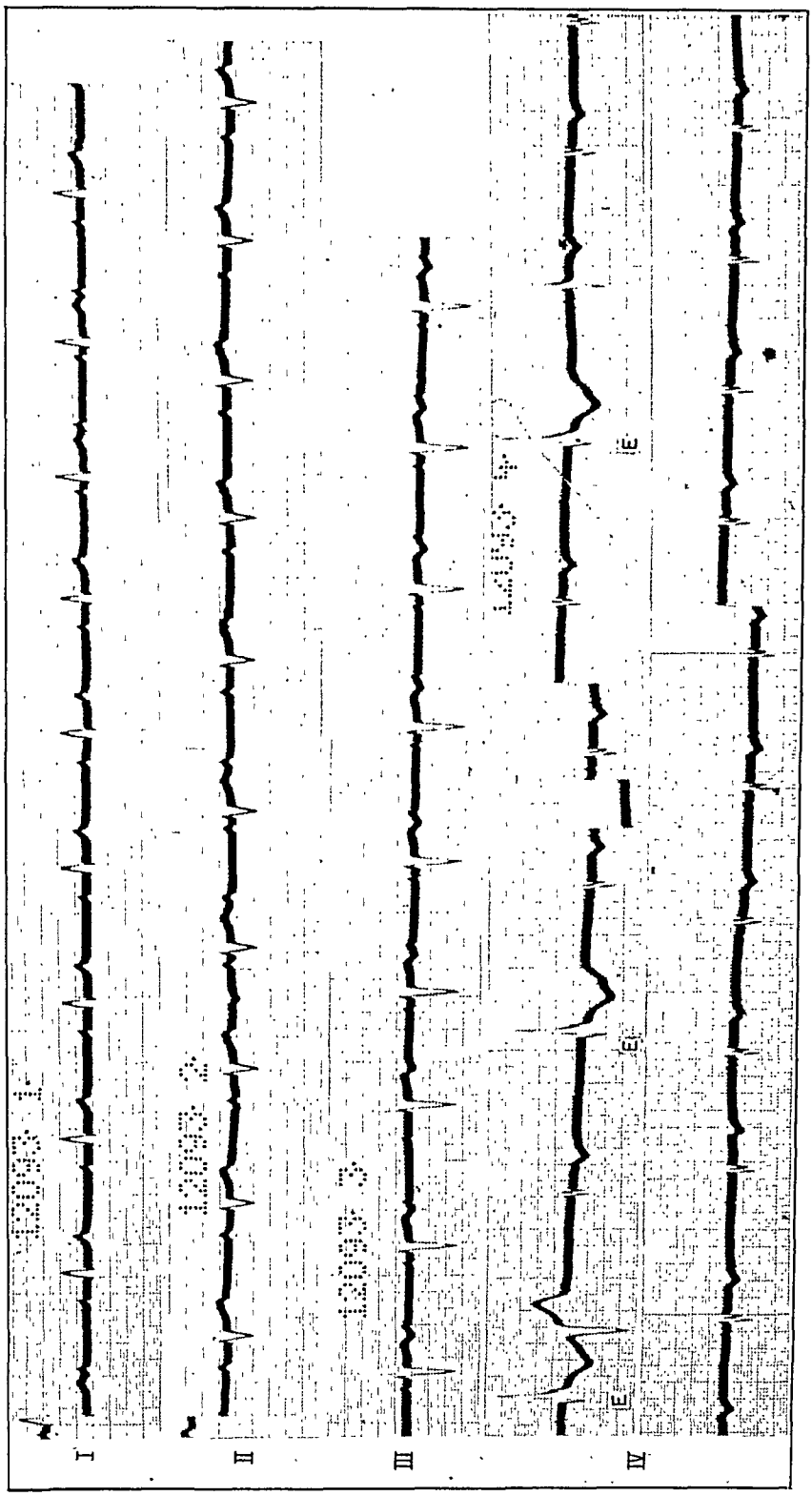

Fig. 2.

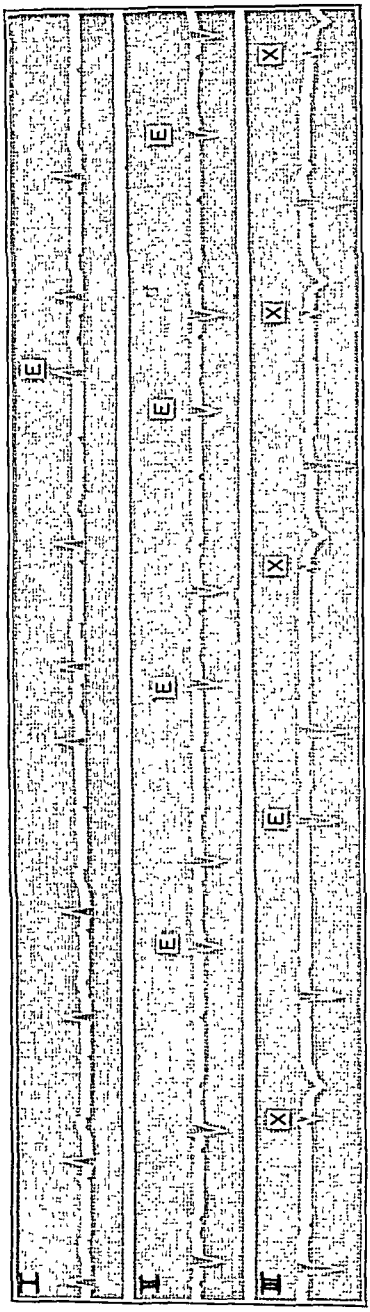

Fig. 3.

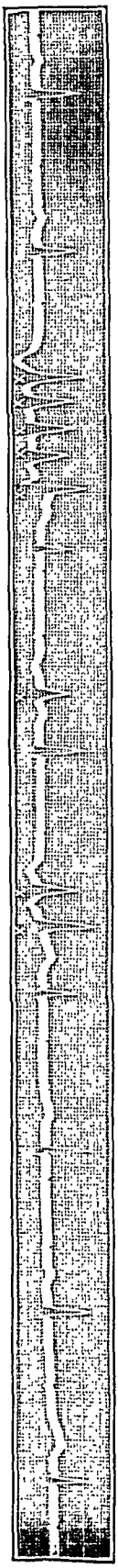

Fig. 4.

every fourth impulse is conducted because of nodal escapes (*E*)* with interference dissociation. In Lead I the third conducted beat has a longer P-R interval (0.36 sec.) than the other conducted beats (0.16 sec.). This is similar to the phenomenon seen in Fig. 2. In Lead III, in addition, the rhythm is complicated further by ventricular premature systoles arising from one focus. The R-R intervals between these extrasystoles is equal to 6.04, 2.84, and 2.86 sec., respectively, which equal 17, 8, and 8 times a cycle length of 0.36 sec. This suggests parasystole with exit block. It would be more convincing if more of these extrasystoles had been seen.

Fig. 4 shows a strip of Lead III taken Aug. 2, 1937. Complete A-V block is now present. (The variation in the contour of the idioventricular complexes may be due to a respiratory shift in the heart's position or to a change in the focus of impulse origin or in the path through which the impulse spread.) In this record a single, a pair, and a run of extrasystoles are shown; this is premonitory of the typical chaos that was to follow.

Fig. 5*A*, Lead III, taken Aug. 3, 1937, depicts clearly the irritability of the ventricular ectopic pacemakers; at least five different types of ventricular complexes appear within an interval of about 5 sec. Fig. 5*B*† and *C*, Lead III, taken Aug. 3 and 9, 1937, respectively, are shown to illustrate the grouping of the ventricular complexes in short runs of tachycardia. Fig. 5*D*, Lead III, taken Aug. 9, 1937, illustrates longer runs of ventricular tachycardia which, in one instance, merge into ventricular fibrillation (or flutter). It is probable that the arrhythmia which was present in this last record was responsible for the patient's shorter syncopal attacks.

TABLE I

P-R INTERVALS IN FIG. 2

LEAD I		LEAD II		LEAD III		LEAD IV	
P-R INTERVAL	DURATION IN SEC.	P-R INTERVAL	DURATION IN SEC.	P-R INTERVAL	DURATION IN SEC.	P-R INTERVAL	DURATION IN SEC.
1	0.16	1	0.36	1	0.16	3	0.38
2	0.34	2	0.36	2	0.16	5	0.14
3	0.34	3	0.36	3	0.34	6	0.14
4	0.34	4	0.16	4	0.17	7	0.36
5	0.34	5	0.16	5	0.16	9	0.14
6	0.34	6	0.34	6	0.17	10	0.14
7	0.32	7	0.36	7	0.16	11	0.14
8	0.15	8	0.36	8	0.16	12	0.14
9	0.15	9	0.36	9	0.16	13	0.36
10	0.34	10	0.36			14	0.16
						15	0.16
						16	0.16
						17	0.16
						18	0.16
						19	0.16
						20	0.16
						21	0.16

*The fifth QRST complex is also a nodal escape; the label *E* was omitted in the reproduction.

†Second strip; the label *B* was omitted in the reproduction.

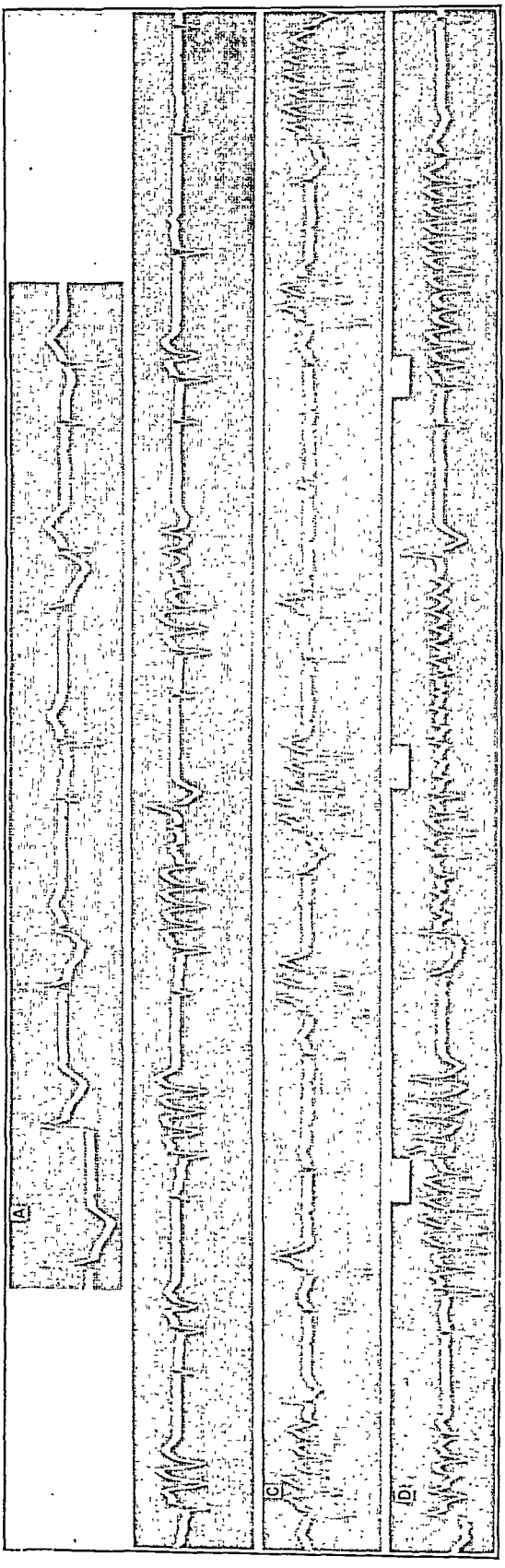

Fig. 5.

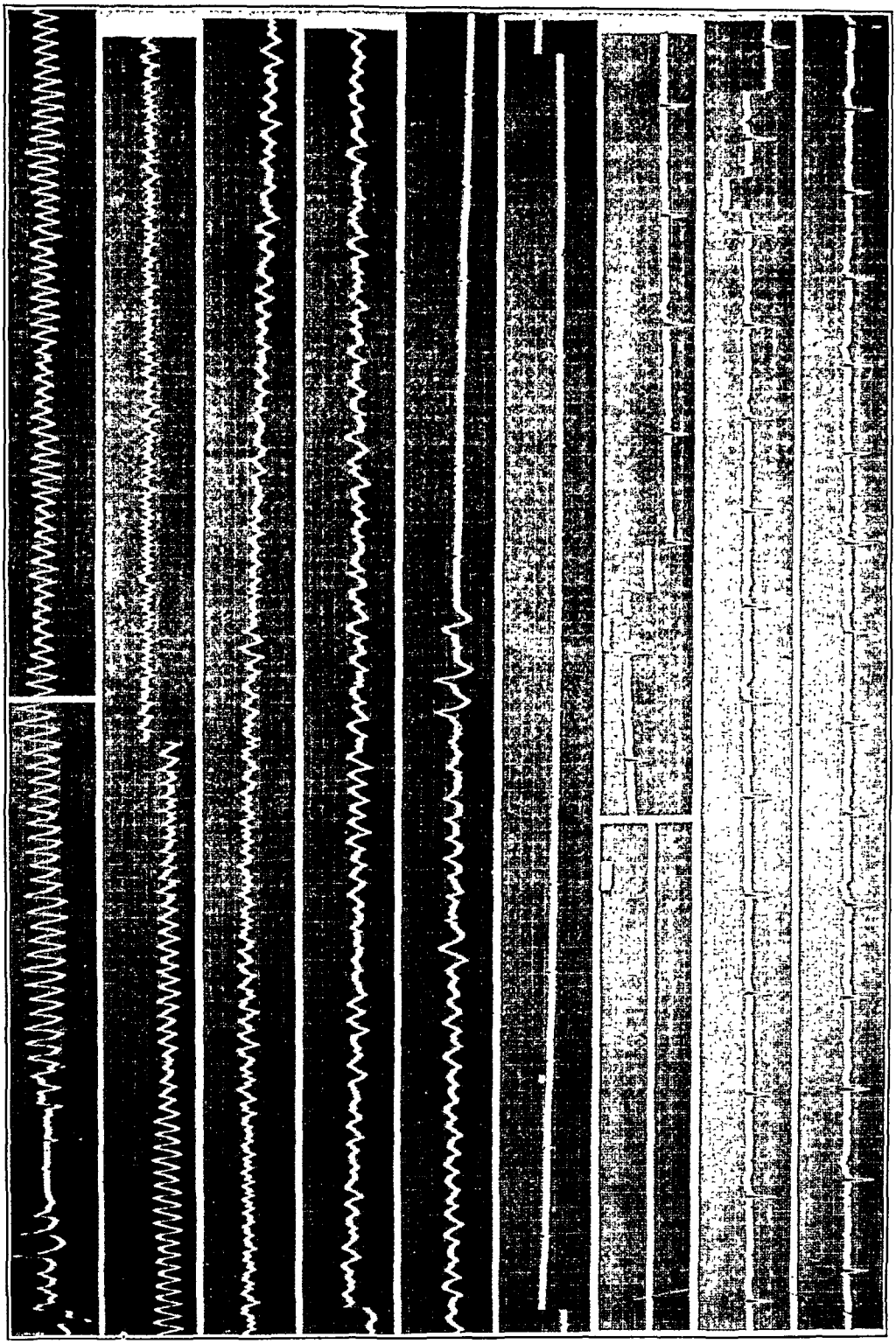

Fig. 6.

Analysis and measurement of a total of 4,500 beats showed that, exclusive of the record in Fig. 6, twenty-six different types of ventricular ectopic beats could be identified. These occurred singly, in pairs, and in runs of three to twenty or more beats, as illustrated in the segments of Fig. 5. Some of these beats appeared to be parasystolic in origin, with or without exit block.[14]

Fig. 6 is a continuous record of Lead III showing the onset, continuation, and termination of a typical long attack which occurred Aug. 10, 1937, at 1:50 A.M. As the seizure started, the heartbeat became very irregular and rapid (about 263 a minute). The patient was extremely restless, crying, and complaining of pain in the legs and abdomen. This prodromal stage, typical of all her attacks, lasted about one-half minute. The record shows the end of the third run of extrasystoles (top strip) and their momentary cessation; they reappear after the next idioventricular beat and are then superseded by flutter of the ventricles at a rate of about 250 per minute. A clonic convulsion which moved the galvanometer string out of the field made it necessary to interrupt the record for a few seconds. When the recording was resumed, coarse ventricular fibrillation was present. At this time the respirations became extremely shallow, then ceased entirely; the patient became extremely cyanotic, her eyeballs rolled upward, and involuntary urination and defecation followed. The pulse became imperceptible, and heart tones were not audible. The fibrillation waves became smaller, more rapid, and then slower and coarser (second, third, and fourth strips and first part of fifth strip). This attack of ventricular fibrillation lasted 1 minute and 23 seconds, and was terminated by three synergic beats, between the last two of which a P-wave is clearly visible (middle of fifth strip). The ventricles then ceased beating for 50 seconds (last part of fifth strip, sixth strip, and first part of seventh strip). During this standstill the auricles continued to beat at a rate of 43 per minute; as the rate increased slightly to 45 per minute the contour of the P-wave changed. The patient appeared lifeless during the ventricular standstill. (As the ventricles commenced to beat, a clonic convulsion threw the string out of the field, causing the gap in the record.) Complete A-V block persisted, but both the ventricular and auricular rates, which were at first slow, became more rapid. With the onset of ventricular activity the pulse gradually became perceptible, and gasping respirations began and were followed by Cheyne-Stokes breathing. The cyanosis disappeared and extreme restlessness and delirium developed. The patient then regained semiconsciousness and complained of pain in her legs and abdomen.

SUMMARY

The case which we have described showed the following unusual features:

A. A period during which 2:1 A-V block was associated with P-R intervals of two durations, one normal (0.15 sec.) and the other prolonged (0.34 sec.). This has not been described previously, as far as we know.

B. Parasystoles of various ventricular origins, occasionally with exit block.

C. Prefibrillatory disturbances with runs of ectopic premature beats from multiple foci which at times developed into transient ventricular fibrillation, causing short attacks of fainting, cyanosis, and Cheyne-Stokes breathing.

D. Longer attacks of unconsciousness and convulsions which were due to ventricular flutter, fibrillation, and standstill. The electrocardiographic record of one such attack is shown.

We are indebted to Dr. Louis N. Katz, under whose guidance this study was undertaken.

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Department of Clinical Reports

INTERMITTENT COMPLETE HEART BLOCK

Report of a Case*

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NOT many authentic cases of intermittent complete heart block, with electrocardiograms, are on record. Carter and Dieuaide,[1] in 1923, collected eight cases from the literature and reported one of their own. In 1934, Weiss and Ferris[2] found that five had been reported since 1923, and added two more in which the block was apparently due to a vago-vagal reflex. In the last few years additional cases have been observed by Dunlap[17] and Sachs and Traynor.[18]

REPORT OF CASE

H. S., a white man 72 years of age, was admitted to the medical service of the Sacred Heart Hospital Oct. 19, 1936, because he had had an attack of syncope. The patient thought that the attack had been caused by weakness and "gas pain in the stomach." His heart was beating regularly at a rate of 50 a minute, and all of the arterial pulses were of equal volume.

For ten years the patient had been subject to fleeting attacks of vertigo without loss of consciousness; in June, 1935, he had his first attack of syncope. Thereafter the attacks recurred at intervals varying from a few hours to six months. Frequently he had been warned of an approaching seizure by a sensation of warmth which arose in the upper abdomen and enveloped the trunk, and he had observed that his pulse rate slowed prior to an attack and accelerated as the symptoms subsided. It is interesting that Cheer and Tang's[4] patient had the same experience and that in Wilson and Robinson's case[3] periods of ventricular standstill were terminated by the sudden onset of a ventricular tachycardia which resembled paroxysmal tachycardia.

Except for an attack of inflammatory rheumatism thirty years earlier, which had confined the patient to bed for four or five weeks, the past history was inconsequential.

Physical Examination.—The skin and mucous membranes were pale, the teeth were carious, and gingival infection was present. The lungs were not demonstrably abnormal. The left border of the heart was 10 cm. from the midline in the fifth intercostal space, and the right border 2 cm. from the midline in the third intercostal space. The heart sounds were inaudible except at the aortic area; no murmurs were heard. The heart rate was 65 a minute, and the blood pressure was 160/80. The peripheral vessels showed signs of sclerosis, as did those of the eye grounds. The reflexes were slightly hyperactive; cutaneous sensations were unimpaired.

Laboratory Examination.—Except for a few leucocytes and a moderate number of hyaline casts, the urine was normal. The hemoglobin was 78 per cent (Dare), and

*From the Electrocardiographic Department of the Sacred Heart Hospital.
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the erythrocytes numbered 3,368,000 per c.mm.; the color index was 0.9. The blood gave negative Kahn, Hinton, and Kolmer reactions. The blood urea nitrogen was 12.1 mg. per cent. The gastric juice contained a normal amount of free hydrochloric acid.

Subsequent Course.—On Oct. 23, 1936, after the patient had had several attacks during which his pulse rate decreased to 20 beats a minute, an electrocardiogram (Fig. 1*A*) showed normal sinus rhythm with a heart rate of 53 per minute, and prolongation of the P-R interval to 0.32 sec. The nature of the seizures, the accompanying bradycardia, and the electrocardiographic evidence of impaired A-V conduction suggested that all of the patient's symptoms had been due to transitory A-V heart block. Extract of belladonna was prescribed in doses of ¼ grain five times a day.

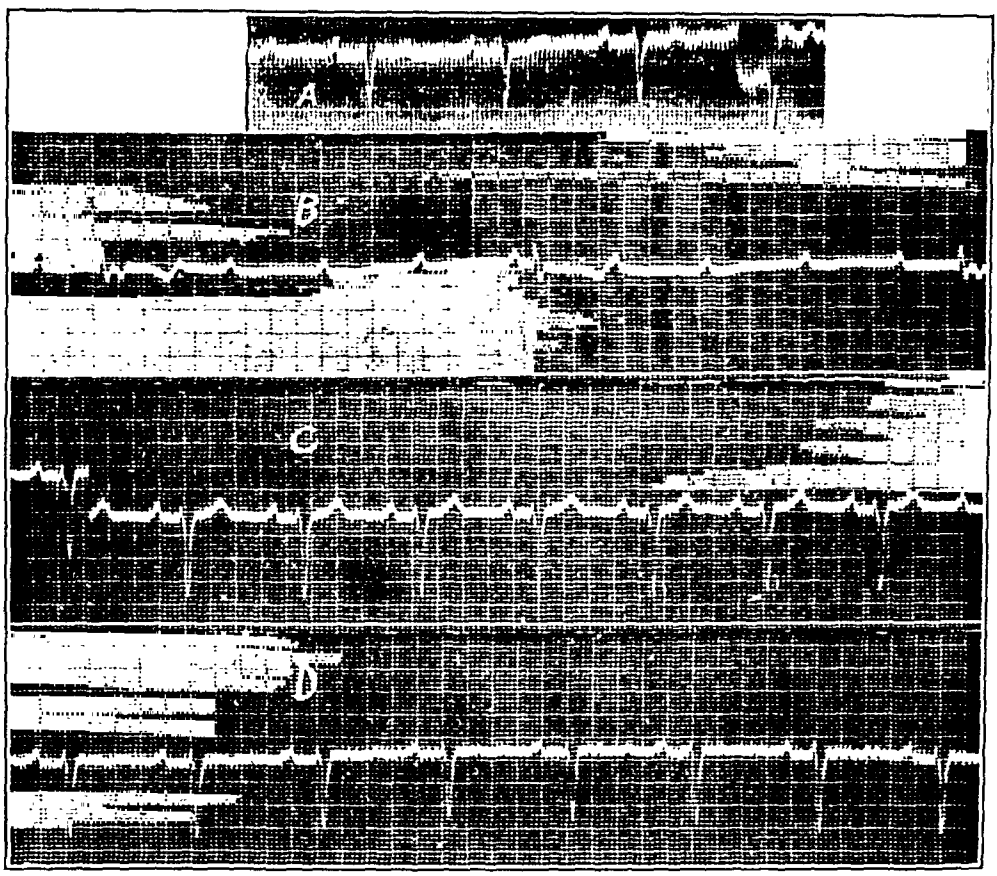

Fig. 1.—*A*, Lead II, taken Oct. 23, 1936. The P-R interval was 0.32 sec.. *B*, Lead II, taken Dec. 12, 1937, showing complete dissociation. *C*, Lead II, taken Dec. 22, 1937. The P-R interval was 0.24 sec. *D*, Lead II, taken Jan. 4, 1938. The P-R interval was 0.28 sec.

Between October 23 and November 3 the pulse rate varied from 52 to 70 a minute, and there were no attacks. On November 3, just as the patient was about to be discharged, he fainted, but recovered quickly, and was allowed to leave the hospital. A nurse who saw him at this time observed that his pulse was "strong and rapid."

The patient was readmitted (service of Dr. W. B. Trexler) Dec. 12, 1937, in a stuporous condition, with a pulse rate of 24 per minute and a blood pressure of 130/40. The subcutaneous injection of 5 minims of a 1:1000 solution of epinephrine roused him, but his pulse rate remained slow. General physical and laboratory examination revealed nothing new. An electrocardiogram (Fig. 1*B*), made several

hours after admission, when all the symptoms of the Adams-Stokes seizure had disappeared, showed complete A-V heart block. Ephedrine sulphate was administered in doses of ⅜ grain every four hours, night and day.

On December 21 the pulse rate was 35 per minute, the blood pressure 160/50, and the patient was having fleeting attacks of vertigo. On December 22, when the patient was free from symptoms, an electrocardiogram (Fig. 1*C*) showed normal sinus rhythm with a P-R interval of 0.24 sec. The remainder of the patient's stay in the hospital was uneventful. An electrocardiogram (Fig. 1*D*), which was made Jan. 4, 1938, showed normal sinus rhythm and a P-R interval of 0.26 sec. The patient was discharged Jan. 7, 1938.

COMMENT

Table I summarizes the important features of the 18 cases of intermittent complete heart block already reported. It will be seen that, in most of those in which electrocardiograms were obtained, the P-R interval after recovery from an attack approached, or exceeded, the upper limit of normal. Because of the comparatively advanced age of most of these patients, the presence of generalized vascular sclerosis in those who came to autopsy, the fact that the heart block eventually became permanent in a number of the cases, and the conspicuous absence of other possible causes, it is reasonable to assume that arteriosclerosis was the principal etiologic factor. Whether or not a superimposed increase in vagal tone, as suggested by Weiss and Ferris,[2] some subtle local circulatory deficiency, as postulated by Carter and McEachern,[5] or still other unknown factors also play a part remains to be seen. That the balance between the normal and abnormal rhythm is delicate is indicated by the prolongation of the P-R interval which is present in many instances during periods of normal rhythm.

The fact that complete heart block may be present when the patient is free from Adams-Stokes attacks, as has been demonstrated by instrumental means in some cases and by clinical methods in others, shows that the heart block alone is not the cause of the attacks. Mackintosh and Falconer,[6] Wilson and Robinson,[3] Cheer and Tang,[4] and Gager,[7] who obtained electrocardiograms preceding and during attacks of syncope, found that the real cause was ventricular standstill. When the mammalian ventricle is suddenly deprived of supraventricular impulses, it is slow to initiate its own rhythm (Erlanger and Hirschfeld[8]), and this latent period is directly responsible for the Adams-Stokes syndrome.

SUMMARY AND CONCLUSIONS

1. A case of transitory complete heart block is reported. The fact that only eighteen cases could be found in the literature indicates that the condition is rare.

2. There is evidence to suggest that coronary arteriosclerosis plays a major etiologic role in this disease, but, with the exception of a few cases in which a vagal reflex seemed to be the precipitating factor, the immediate cause of the recurrent heart block and of the ventricular asystole which is responsible for the Adams-Stokes syndrome is not known.

TABLE I

AUTHOR	AGE	SEX	BLOOD PRESSURE		VENTRICULAR RATE		AURICULAR RATE	AC INTERVAL		P-R INTERVAL		VENTRICULAR STANDSTILL (SEC.)	ADAMS-STOKES	AUTOPSY FINDINGS
			DURING ATTACK	AFTER ATTACK	REGULAR SINUS	DURING ATTACK		BEFORE ATTACK	AFTER ATTACK	BEFORE ATTACK	AFTER ATTACK			
Earnshaw[9]	53	M			80-90	11-12	33-90	0.2	0.2				Present	
Gossage[10]	71	F		200/--	60			0.2	0.2				Present	
Cohn, Holmes and Lewis[11]	80	F				27-29		0.2	0.2				Present	Sclerosis of A-V node
Mackintosh and Falconer[6]	74	M			56							11	Present	
Lewis[12]	48	M						0.2	0.2			3- 8	Present	
Wilson and Robinson[3]	48	F				90	120			0.20	0.38	7-11	Present	
Starling[13]	51	M			60-80	43	110	0.2	0.2				Present	
Russell-Wells and Wiltshire[14]	44	M			62-74		51			0.20	0.20		Present	Cardiac sclerosis
Carter and Dieuaide[1]	70	M	128/60	130/85	78	30	78			0.17	0.18		Present	
Kahler[15]	30	F	80-90/--	100-115/--	64-80								Present	
Gager and Pardee[16]	59	M		150/75	60	15-27	92-94				0.16	6-20	Present	Calcareous change in bundle
Carter and McEachern[5]	63	M	180/65	140/90		20	63			0.18	0.16	6-20	Present	
Cheer and Tang[4]	66	M		120/60	83	18	120						Present	
Dunlap[17]	57	M			84	22-63					0.24		Absent	
Gager[7]	80	M	160/90	140/86	65-72	41	75			0.18	0.16		Present	
Sachs and Traynor[18]	43	M		130/80	68-88	17-19				0.17	0.24		Present	
Weiss and Ferris[2]	64	M	94-140/56-80		48-66					0.19 0.20	0.19 0.20		Present	
Weiss and Ferris[2]	28	F											Present	

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THE ACUTE COR PULMONALE

Report of a Case Occurring Eleven Days Post Partum

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DURING the past two years the growing recognition of the importance of electrocardiographic changes which may be associated with acute pulmonary embolism has aroused the interest of the surgeon no less than that of the internist. It has resulted, too, in the formulation of fairly definite diagnostic criteria which may serve to differentiate the acute cor pulmonale (dilatation of the pulmonary artery and right heart chambers) from the acute coronary accidents which, clinically, it may simulate. Since the earlier work of McGinn and White,[1] Barnes[2] has contributed additional electrocardiographic data, and Gibbon and Churchill[3] have done much by their experimental studies to clarify our concept of the physiology of the disease.

The case presented below correlates many of the observations previously noted, and in addition represents, we believe, the first electrocardiographic record published of this serious complication occurring post-partum. It should, then, be of interest to the obstetrician.

It will be noted that the chest lead of each record has been obtained by placing the left leg electrode over the cardiac apex, and by utilizing the left arm plate* as the indifferent electrode with the electrocardiographic switch at Lead III. Normally this arrangement yields an upward initial deflection of the QRS complexes and upright T-waves in contrast to the corresponding negative deflections of the former chest lead first introduced by Wolferth.

REPORT OF CASE

A 29-year-old white American housewife was admitted to the hospital Aug. 15, 1937, to be delivered of a child. She had had four normal pregnancies in the preceding eight years, the first two terminating by midforceps delivery, the third and fourth normally. Convalescence in each case had been uneventful.

Physical examination showed no abnormalities except obesity. The blood pressure was 130/90. The abdominal findings were those of full-term pregnancy. After twelve hours of labor with little progress she was given 3 minims of pitressin, and labor terminated an hour later under nitrous oxide-oxygen-ether anesthesia. The placenta and membranes were delivered intact by mild Credé. There was moderate hemorrhage. During the next few days the patient seemed rather depressed at times and complained of tenderness over the bladder and dysuria. The urine showed only a few leucocytes per high-power field; the fundus was firm; and the lochia

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*On left arm in this case, although it may be placed on left leg, right arm, or back with little variation.

was rather less than moderate. On the tenth day the patient felt well and strong, ate and slept well, and had no further bladder trouble; the lochia was scant, the fundus was firm, and when she was allowed to sit up for a short time, there were no untoward symptoms.

About eight o'clock the next morning—August 26—eleven days post partum, while sitting in bed, the patient reached for an article of clothing preparatory to getting up. Just as she did so she felt very faint, broke out in cold perspiration, and fell back upon her pillow with a cry for help. She thought she was going to die and struggled against a feeling of suffocation which seemed to sweep upward over her body, localizing substernally and in her midscapular region as an intense

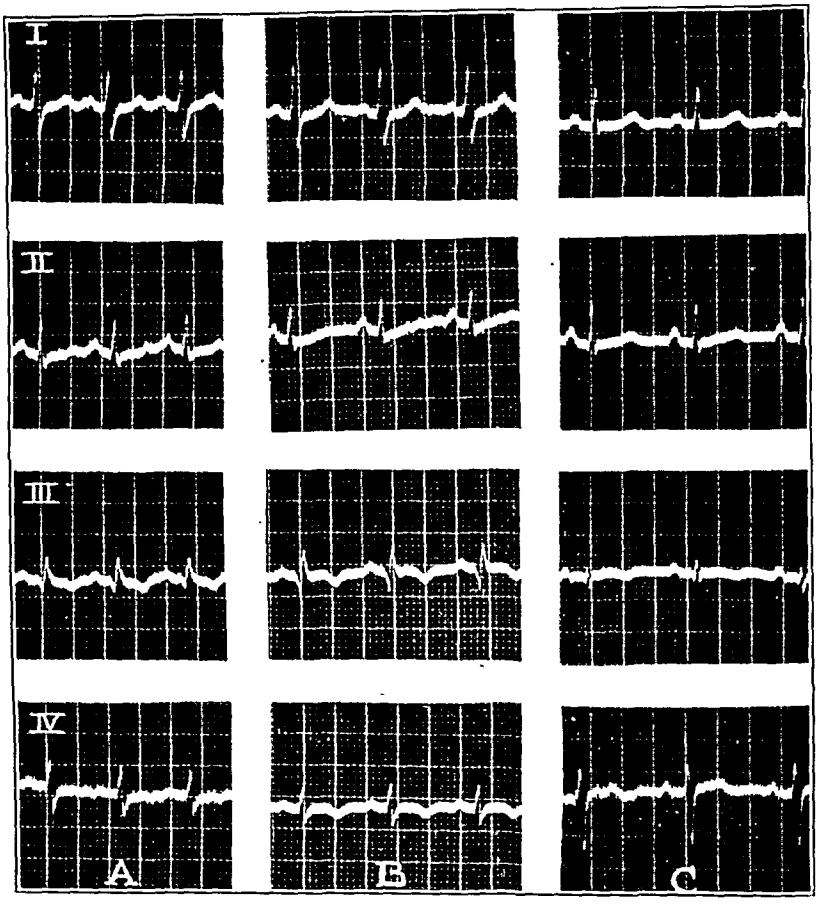

Fig. 1.—Electrocardiograms of the acute cor pulmonale. *A*, one-half hour after onset of symptoms, showing a deep and slurred S-wave in Lead I, a low diphasic T-wave with slight depression of the S-T origin in Lead II, the presence of Q_3, and shallow late inversion of T_3 with just a suggestion of convexity of the S-T_3 segment. Lead IV shows relatively low voltage, and T_4 is practically isoelectric. *B* shows a progression of the changes noted above during the next twenty-four hours, and *C* shows a return toward the normal one week after the acute attack.

oppressive pain. When seen a moment later by the nurse she was very pale, apprehensive, and perspiring freely. Her pulse rate, which had been 60 to 70 before the attack, was 56, her blood pressure was 110/70, and her respirations were rapid and labored. When seen by her physician fifteen minutes later the pulse rate was 112, the pulse was rather weak but regular, and her color was a little better. The respirations were still rapid and painful, but the feeling of oppression and suffocation was less intense. One-half hour later there was a marked systolic gallop rhythm the maximum intensity of which was along the right sternal border. The pulmonic second sound was not accentuated, no murmurs were audible at the base

of the heart, and there was no distention of the cervical veins, pulmonary edema, or hepatic engorgement. She had no cough and raised no sputum. The first electrocardiogram (Fig. 1*A*) was taken at this time. The leucocytes numbered 10,000; 87 per cent were neutrophiles, 10 per cent lymphocytes, 2 per cent eosinophiles, and 1 per cent monocytes.

Two and one-half hours after the onset of her symptoms the patient stated that the feeling of pressure in her chest became less rather abruptly and that the pain between her shoulders "shifted downward," allowing her to breathe more easily. During the next twelve hours the feeling of oppression recurred at intervals in spite of the administration of morphine on two occasions. She perspired profusely and was quite nervous. Her pulse rate varied around 140 much of this time, her temperature was 99.4° F., and her blood pressure was 110/68. The following morning, twenty-four hours after the onset of her attack, she had no discomfort so long as she lay quietly. The temperature was 99° F., the pulse rate 108, the respiratory rate 20, and the blood pressure 110/78. The heart sounds were of better quality, the gallop rhythm had disappeared, and there was a faint systolic murmur of about equal intensity at apex and base. A second electrocardiogram (Fig. 1*B*) was taken. During the next week she showed marked improvement. A roentgenogram of the chest taken with a portable apparatus four days after her attack showed slight increase in the density of both hila; there was no undue prominence of the pulmonary conus.

One week after the onset of acute symptoms a third electrocardiogram (Fig. 1*C*) was taken. Physical examination revealed no abnormalities except a slight, but definite, accentuation of the pulmonary second sound, and the presence of a soft basal systolic murmur which was of about equal intensity along both sternal borders and was transmitted laterally—to the right about 5 cm. and to the left about 3 cm. No thrills were palpable, and there was no increase in the area of cardiac dullness. The patient remained symptom-free, sat up for a short time on the twelfth day after her attack, and went home two days later.

DISCUSSION

The electrocardiographic tracing (Fig. 1*A*) taken one-half hour after the onset of this patient's symptoms, while she still had signs of shock, shows a deep and slurred S-wave in Lead I; the T-wave in Lead II is low and diphasic with slight depression of the S-T origin; Q_3 is present; and T_3 shows shallow late inversion with just a suggestion of convexity of the S-T_3 segment. The chest lead shows relatively low voltage, and T_4 is practically isoelectric.

Twenty-four hours later these initial changes are more marked. (Fig. 1*B*.) Lead I appears much the same (deep and slurred S-wave), but T_2 is now practically flat, Q_3 is more prominent, and T_3 shows well-marked late inversion with convexity of the S-T_3 segment. The voltage in the chest lead is even lower than in the preceding record, and T_4 shows shallow late inversion with convexity of the S-T_4 segment. The patient had no pain at this time, though she complained of mild substernal discomfort if she attempted to move about.

One week later the electrocardiogram (Fig. 1*C*) shows relative prominence of the P-waves, but S_1 has entirely disappeared, T_2 is low but definitely upright, T_3 shows very shallow inversion, the voltage of the

chest lead is quite normal, and T_4 is flat or slightly diphasic with convexity of the S-T_4 segment. It is of interest to note that the initial deflection of QRS_3 is now upright.

SUMMARY AND CONCLUSION

A twenty-nine-year-old housewife, eleven days after the birth of her fifth child, suddenly collapsed as she was reaching for her clothing preparatory to getting out of bed. Air hunger, a feeling of impending death, and substernal oppressive pain were the outstanding symptoms. Objectively she presented the characteristic signs of shock. Such clinical manifestations of acute pulmonary embolism are all too familiar to the obstetrician, but the above case is presented to illustrate the fact that when such an embolus suddenly obstructs the pulmonary artery or its main branches sufficiently to cause dilatation of the right side of the heart, the symptoms and signs may closely simulate those of acute coronary occlusion. As has been pointed out in other papers and by other authors,[1, 2, 4] the electrocardiographic records may also simulate in many respects those obtained following acute myocardial infarction in the posterior basal region of the left ventricle. There are significant differences, however, in particular the appearance of S_1 and inversion of T_4, and it is felt that the accumulation of data will serve to emphasize these differences and enable us to establish criteria for accurate diagnosis when clinically such differentiation is less obvious.

REFERENCES

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White, Paul D.: The Acute Cor Pulmonale, Ann. Int. Med. 11: 115, 1935.
2. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. 9: 11, 1936.
3. Gibbon, J. H., Jr. and Churchill, E. D.: The Physiology of Massive Pulmonary Embolism; An Experimental Study of the Changes Produced by Obstruction to the Flow of Blood Through the Pulmonary Artery and Its Lobar Branches, Ann. Surg. 104: 811, 1936.
4. Langendorf, R., and Pick, A. (Prag): EKG—Befunde bei Lungenembolie, Acta Medica Scandinav. 90: 1-111, 1936.

Department of Reviews and Abstracts

Selected Abstracts

Zettler, L.: The Action of Vasomotor Acting Drugs on the Permeability of Arteries. Arch. f. exper. Path. u. Pharmakol. 185: 141, 1937.

Increased arterial wall permeability was produced by diuretics, and also to a lesser extent by nitrites. Calcium and nicotine decrease the permeability.

KATZ.

Fröhlich, A., and Zak, E.: The Ability of the Lungs to Regulate the Water Content of the Blood. Arch. f. exper. Path. u. Pharmakol. 185: 277, 1937.

The authors were able to demonstrate a *perspiratio insensibilis negativa* in the lungs. They found that from twenty to thirty minutes after glycerin was injected into the peritoneal cavity of rabbits, with consequent exudation and concentration of blood, that the blood obtained from the left ventricle was more dilute than that from the right ventricle, indicating a passage of water from alveolar air into the blood. This dilution did not occur when the observations were made on rabbits anesthetized with ether, urethane, pernocton, or with large doses of morphine, nor in decerebrated animals. When dry O_2 was used as an inhalant, this dilution of blood by lung was absent, but not when moistened O_2 was used.

KATZ.

Ratschow, M.: Exercise Test for Determining Peripheral Arterial Blood Flow Disturbances. München. med. Wchnschr. 84: 1128, 1937.

An ergometer was used with which the foot is made to do standardized rate of work. The amount of work before pain occurred was determined. The normal value was established, and this was found to decrease with age. This method distinguishes pain due to arterial disease from other types of limb pain, since in the former there is a latent period before pain appears.

KATZ.

Zeus, L.: Experimental Investigations on Goiter Hearts Following Thyroxin Injections. Arch. f. Kreislaufforsch. 2: 165, 1938.

Morphologic and histologic changes were obtained in the hearts of eight rabbits following the injection of thyroxin from 6 to 249 days. This consisted of the enlargement of the right auricle and hypertrophy of the right heart and eventually of the left ventricle also. The degree of change depended on the dose and period of days during which the hormone was administered. In addition, fatty parenchymatous degeneration of the heart muscle and fibrous replacement with interruption of muscle fibers accompanied by slight lymphocytic infiltration were found microscopically.

KATZ.

Katz, L. N., Jochim, K., and Bohning, A.: The Effect of the Extravascular Support of the Ventricles on the Flow in the Coronary Vessels. Am. J. Physiol. 122: 236, 1938.

A method is described for measuring total coronary inflow and coronary sinus outflow in a completely denervated heart-lung or isolated heart preparation in which the coronary arteries are perfused with blood at constant pressure, and all other variables are controlled. The following were the chief results obtained in this preparation:

Changes in heart rate alone do not appreciably alter the rate of the total coronary blood flow.

The rate of total coronary blood flow varies directly with the coronary perfusion pressure, other conditions being constant.

When all other variables are kept constant, the total coronary inflow is decreased by raising the mean pressure within the heart cavities and thus the mean intramuscular tension within their walls. Decreasing these pressures increases the total coronary inflow. This change in coronary inflow can be effected by varying the pressures and tensions of each side of the heart alone.

When the mean pressure of the heart cavities is changed, the rate of sinus outflow varies in a direction opposite to the total coronary inflow, so that the ratio between the two varies widely. Changes in sinus outflow depend almost entirely on changes in pressure in the right side of the heart, the pressures in the left side having little effect.

The coronary sinus outflow may persistently exceed the total coronary inflow when the mean pressure in the heart cavities and the mean intramuscular tension of their walls are high relative to the coronary perfusion pressure; changes in the pressure in the right heart are more effective than in the left in this regard.

The significance of these findings is discussed. It is pointed out among other things (1) that the coronary sinus outflow cannot be used as a measure of the total coronary flow and (2) that significant passive changes in the caliber of the coronary vessels are produced by altering the extravascular tension in the heart walls and that this factor as well as variations in the aortic pressure must be ruled out before changes in coronary inflow can be ascribed to active changes in the tone of the muscles in the coronary vessel walls.

AUTHOR.

Katz, L. N., Jochim, K., and Weinstein, W.: The Distribution of the Coronary Blood Flow. Am. J. Physiol. 122: 252, 1938.

A method is described for measuring total coronary inflow, drainage from the coronary sinus, drainage from the Thebesian vessels and accessory veins of the right heart, and drainage from the Thebesian vessels and accessory veins of the left heart in an isolated, fibrillating dog's heart with the three main coronary branches perfused with defibrinated blood at constant pressure and temperature. The results of twelve experiments are reported.

The proportion of total coronary flow carried by each of the three main coronary arteries (left circumflex, anterior left descending, and right circumflex) was found to be widely variable in different individuals.

Evidence is presented to show the probable existence of functional anastomoses between the three main coronary arteries in some animals.

The proportion of total outflow carried by each of the three drainage channels was found to be widely variable in different individuals. In particular, the proportion drained by the coronary sinus varied from 17 per cent to 44 per cent with an

average of 32 per cent. These results are not in accord with the almost constant sinus drainage of 60 per cent reported by Anrep, Blalock, and Hammouda.

The differences in coronary sinus drainage between the beating and fibrillating heart are discussed.

The distribution of blood from each of the three main coronary arteries of each of the three drainage channels was found to be widely variable in different individuals.

The invalidity of using coronary sinus outflow as an index of total coronary flow is further substantiated.

AUTHOR.

Page, Irvine H.: The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs With Experimental Hypertension. Am. J. Physiol. 122: 352, 1938.

The adrenal cortex plays an important part in the mechanism responsible for development of hypertension in dogs by constricting the renal arteries. The adrenal medulla does not appear essential.

Neither the ovaries nor the testes are essential for the maintenance of hypertension in dogs with their renal arteries constricted.

Administration of maintenance doses of adrenal cortical extract and possibly salt is necessary for persistence of moderate hypertension in dogs with both renal arteries constricted and the hypophysis, testes, and adrenal glands removed.

The opinion is offered that endocrine glands in hypertensive animals of this type are concerned chiefly with maintenance of the body in such a state that it can respond to constriction of the renal arteries by development of arterial hypertension.

AUTHOR.

Burn, V. H.: Sympathetic Vasodilator Fibers. Physiol. Rev. 18: 137, 1938.

Lewis and Pickering (1931) brought forward evidence for the existence of a sympathetic vasodilator supply to the skin of man. Uprus, Gaylor, and Carmichael (1936), however, do not appear to be satisfied that the conclusion drawn by Lewis and Pickering was sound. The existence of sympathetic vasodilator fibers in human skin must still be regarded as doubtful. In man the question of whether there are sympathetic vasodilator fibers elsewhere than in the skin has not, for technical reasons, been studied. In animals recent work has shown that there are important differences in different parts of the body and in different species. For instance, in the rabbit and monkey there are no sympathetic vasodilators to the muscles; in the cat there are a few, while in the dog and in the hare there are many. The effect of stimulating the sympathetic supply to the muscles of the hare is a curious mixture of constriction and dilatation; had our knowledge of the sympathetic control of the blood vessels been based on the hare instead of the cat, current teaching might have been entirely different.

MONTGOMERY.

Nelson, Erwin E., and Calvery, Herbert O.: Present Status of the Ergot Question. Physiol. Rev. 18: 297, 1938.

Most of this review article deals with the chemistry and pharmacology of various ergot preparations. Gangrenous ergotism is dealt with only very briefly. Gangrene in man seems to have been proved to occur as a result of ergot alkaloids. Its most frequent occurrence is in cases of puerperal sepsis treated with ergotamine.

MONTGOMERY.

Laurell, H.: The First Heart Sound. Ztschr. f. Kreislaufforsch. 30: 209, 1938.

The author presents his arguments in support of the view that the first sound is caused by the squeezing out of blood within the heart walls during systole. This normally occurs during the isometric contraction phase.

KATZ.

Anthony, A. J., and Harlandt, W.: Respiratory Arrhythmia in Hypoxemia. Ztschr. f. Kreislaufforsch. 30: 241, 1938.

When a subject with sinus arrhythmia is placed in a compression chamber and the pressure in it decreased, the sinus arrhythmia decreases as the pulse rate accelerates, and it finally disappears at a pressure equivalent to an altitude of 3,000 to 5,000 meters above sea level. This was found to be the case in thirteen subjects.

KATZ.

Müller, E. A.: Cardiac Work and Heart Volume. Arch. f. ges. Physiol. 238: 638, 1937.

In the heart-lung preparation the author showed that at constant minute volume output the diastolic volume of the right heart is increased from three to nine times as much as that of the left heart by a similar increase in the peripheral resistance against which each chamber works. Increasing the minute volume output of the heart at constant peripheral resistance has no effect on systolic heart size. Increasing the mechanical work of the left heart by increase in aortic pressure while keeping the minute volume output constant increases the size of the left heart twenty times as much as a similar increase in work produces when caused by an increase in minute volume output without a change in arterial pressure.

KATZ.

Zaeper, G.: Determination of the Circulation in Health and in Heart Disease. Deutsche med. Wchnschr. 63: 417, 1937.

Trained individuals at a given rate of oxygen consumption show a greater venous oxygen unsaturation than untrained individuals. This indicates that in the former the rate of blood flow, and hence the work of the heart, is less than in the latter. Calculations show that in exercise the work of the heart is 2.4 times as great in untrained as in trained individuals. Training of the cardiac patient can serve, therefore, to decrease the load on the heart.

KATZ.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: II. Pulsations Associated With Tricuspid Regurgitation. Arch. Int. Med. 60: 437, 1937.

A diffuse systolic depression of the anterior wall of the chest is found in instances of aortic regurgitation. This is a result of the increased stroke volume of the left ventricle, unless the aspiratory effect, owing to reduction of the ventricular volume during the systolic efflux, is neutralized by the opposing forces due to the systolic change in shape of the heart. In other instances there is no movement of the thoracic wall adjacent to the liver, while a distinct systolic depression is noted over the precordium. The diastolic pulsation of the thoracic wall in aortic insufficiency takes place slowly, as contrasted with the speed noted in the majority of cases of adhesive pericardial disease or tricuspid regurgitation, in which an abrupt propulsion of the thoracic wall is noted during diastole.

AUTHOR.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: III. Pulsations Associated With Tricuspid Regurgitation. Arch. Int. Med. 60: 441, 1937.

As in cases of aortic regurgitation, one finds in many instances of tricuspid regurgitation a diffuse systolic depression of the precordium. This is caused by the complete emptying of the right ventricle.

The aspiratory effect on the thoracic wall due to the reduction of the ventricular volume during the systolic efflux is particularly pronounced in tricuspid regurgitation, since the dilated right ventricle empties during systole in two directions simultaneously. In addition, the most important factor for the neutralization of the systolic fall of the intrathoracic pressure, i.e., the influx of venous blood, is eliminated by regurgitation into the veins. Regurgitation into the liver leads to a forceful propulsion of the right upper and lower portions of the chest and occasionally also to a jerky shift of the whole chest from left to right; the latter finding is particularly characteristic of this type of valvular lesion. The propulsion of the right side of the chest in association with the systolic depression over the cardiac area results in a seesaw movement, which Vollhard was the first to describe for tricuspid regurgitation. No significance should be attributed to the systolic filling of the right auricle in the etiology of this pulsatory phenomenon.

In contrast to aortic regurgitation, the apical thrust is absent as a rule in cases of tricuspid regurgitation. This is due to the fact that the left ventricle is poorly filled and is pushed away from the anterior wall of the chest by the much enlarged right ventricle. There is forceful filling of the right ventricle because of the high venous pressure, and occasionally one finds an abrupt diastolic pulsation of the thoracic wall, very similar to the diastolic cardiac thrust in the presence of adhesive pericardial disease. Likewise, Friedreich's reduplicated sound is occasionally heard. Confusion of tricuspid regurgitation with adhesive pericardial disease is therefore not uncommon, and only a careful observation of the forceful hepatic regurgitation pulse will insure against diagnostic error.

The systolic depression is often inhibited in the presence of a combination of tricuspid regurgitation with mitral stenosis, because of the opposing force of the change in shape of the heart.

AUTHOR.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: IV. Pulsations Associated With Adhesive Pericardial Disease. Arch. Int. Med. 60: 654, 1937.

Diffuse pulsations of the thoracic wall in the presence of adhesive pericardial disease are by no means necessarily associated with external adhesions. Two factors play the main role: (1) an inhibition of the systolic change of shape of the heart whereby the aspiratory forces due to reduction of the ventricular volume during the systolic efflux prevail and (2) a change in the mechanism of volumetric diminution so that the marginal movements of the ventricles prevail because the longitudinal shortening of the ventricular cone is inhibited. Fluoroscopy in instances of obliterative pericardial disease associated with marked depression of the thoracic wall does not necessarily reveal a diminution of the marginal movements of the silhouette, as commonly accepted, but, on the contrary, rather strikingly large amplitudes may be observed.

The inhibited systolic change in the shape of the heart due to internal adhesions is of decisive importance for the appearance of a diastolic propulsion of the thoracic wall. External adhesions are not a prerequisite.

Similar to tricuspid regurgitation, adhesive pericardial disease is not rarely accompanied with a pulsatory movement of the whole chest directed from left to right

during systole; this is due to a pulsatory associated movement of the right side of the chest. Tricuspid regurgitation is differentiated from adhesive pericardial disease by the absence in the latter of a forceful systolic hepatic regurgitation pulse.

AUTHOR.

Dressler, Wilhelm: Pulsations of the Wall of the Chest: V. Pulsations Associated With Mitral Regurgitation and Aneurysmal Dilatation of the Left Auricle. Arch. Int. Med. 60: 663, 1937.

A pulsating propulsion of the right wall of the chest is observed in cases of aneurysmal dilatation of the left auricle to the right. Mitral regurgitation is a prerequisite, and the pulsations are caused by the impact of the blood regurgitating into the left auricle. The maximum of these pulsations as a rule is found in the right midclavicular line between the fourth and the sixth rib, and pulsations may be observed as far as the right axilla.

AUTHOR.

Bruger, Maurice: Cholesterol Content of the Blood in Heart Disease. Arch. Int. Med. 61: 714, 1938.

There is a marked difference between the cholesterol content of the plasma of patients with rheumatic heart disease and that of patients with arteriosclerotic or hypertensive heart disease. Patients with rheumatic heart disease frequently demonstrate hypocholesteremia, although for all the patients as a group the results lack statistical significance when compared with the cholesterol content of the blood of normal subjects. In contrast is the hypercholesteremia often observed for patients with arteriosclerotic heart disease or hypertensive heart disease manifesting some evidence of arteriosclerosis; for these two groups, however, the increase in the plasma cholesterol value is of sufficient magnitude to be statistically significant. For the most part, there is little or no difference between the ratio of ester to free cholesterol in the three types of heart disease studied.

AUTHOR.

Greene, James A., and Swanson, L. W.: Clinical Studies of Respiration: VI. Expiratory Inflation During Air Hunger and Dyspnea Produced by Physical Exertion in Normal Subjects and in Patients With Heart Disease. Arch. Int. Med. 61: 720, 1938.

The expiratory volume of the chest has been studied during hyperpnea produced by physical exertion in normal subjects and in patients with heart disease. The increase observed in all instances was of greater degree and proportionately of longer duration in the patients. These results indicate that expiratory inflation per se is not the major factor in the production of air hunger and dyspnea in cases of cardiac failure.

AUTHOR.

Donal, John S.: A Convenient Method for the Determination of the Approximate Cardiac Output in Man. J. Clin. Investigation 16: 879, 1937.

A simplified oxygen method has been developed by which the cardiac output of either normal or clinical subjects may be estimated from a determination of metabolism and the analysis of the oxygen and carbon dioxide contents of only two samples, collected during a single rebreathing procedure.

The effects of various errors inherent in the assumptions and technique have been investigated. Experimental results have shown that many of these errors are so

small that they may be neglected. From calculations, and from a consideration of the work of other investigators, it has been concluded that the influence of the remaining apparent errors is likewise relatively unimportant.

The averages of estimations of basal cardiac output by the new procedure have been found to be in good agreement with the averages of determinations made on the same normal and clinical subjects by the ethyl iodide method of Starr and Gamble and by the acetylene method of Grollman. The agreement of estimations by the three methods on individual subjects is not very good, a result to be expected from the known variation of duplicate estimations in many subjects. In seven instances the result of the oxygen method agreed more closely with the average of the ethyl iodide results than with the result of the single estimation by acetylene. In three instances the oxygen result was closer to that obtained by acetylene.

Duplicate estimations by the oxygen method agreed more closely than similar duplicates made by ethyl iodide in four patients.

AUTHOR.

Bohning, A., and Katz, L. N.: Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion. Arch. Int. Med. 61: 241, 1938.

We have reported on 200 cases of coronary occlusion studied for three years. We have made a careful detailed analysis of the incidence of various abnormalities in the standard three leads and the deviations of Lead IV in cases of (a) recent anterior infarction, (b) recent posterior infarction, and (c) combined anterior and posterior infarctions. The criteria for this division according to the type of infarction were based on the characteristic electrocardiographic deviations in our own and in other cases in which the diagnosis was verified at autopsy.

We have presented illustrations of the four-lead electrocardiograms in 25 cases of recent infarction together with the pertinent autopsy data. Similar data are presented for 2 cases of recent small multiple infarcts and for 8 cases of coronary sclerosis without infarction. We have illustrated with actual serial curves and with diagrams the evolution of the classical changes in cases of recent anterior and posterior infarction due to thrombosis.

We have demonstrated the differences in the electrocardiogram in cases of recent infarction due to suddenly occurring coronary thrombosis and in cases of infarction due to slowly occluding sclerotic plaques.

We have, as a result of these studies, reached the following conclusions:

The incidence of all types of myocardial infarction due to coronary occlusion is greater in men than in women, and the incidence of anterior infarction is greater than that of posterior infarction. The mortality from posterior infarction is relatively less than that from other types.

Septal involvement occurs with all types of myocardial infarction, but it is relatively more frequent with anterior infarction. If the septal infarction is near the apex, intraventricular block may not appear in the electrocardiogram.

Low "voltage" in the standard three leads occurs relatively more often with anterior infarction, but Lead IV is usually not affected.

Preponderance of the left ventricle is most often associated with posterior infarction but may occur with anterior infarction.

Lead IV is of definite aid in the diagnosis of recent myocardial infarction due to coronary occlusion, especially anterior infarction.

The frequency of the various types of recent myocardial infarction is more in accord with autopsy statistics when four leads are used than when only the three limb leads are used.

AUTHORS.

de Boer, S.: The Stokes-Adams Syndrome. Cardiologia 1: 253, 1937.

The author described in previous investigations two different kinds of Stokes-Adams syndrome:

1. Stokes-Adams complex in cases of ventricular fibrillation, often occurring in patients with total heart block (Ztschr. f. d. ges. exper. Med. 38: 191, 1923).

2. Stokes-Adams complex in cases of Luciani's periods, often together with total heart block. Stokes-Adams period is in this case caused by periods of standstill of the ventricles or of the whole heart (Ztschr. f. d. ges. exper. Med. 83: 1, 1932).

The author draws attention to a third possible cause of Stokes-Adams complex, namely, the sudden onset of ventricular pulsus bigeminus; in this condition the ventricular extrasystoles arise at a time when the ventricle contains very little or no blood. The number of beats is suddenly reduced to half its previous rate. The author describes two cases of this type; there was no heart block. The prognosis in these cases is not as serious as for the other types.

AUTHOR.

Sigler, Louis H., Stein, Isidore, and Nash, Philip I.: Electrocardiographic Changes Occurring at Death. Am. J. M. Sc. 194: 356, 1937.

Electrocardiographic studies were made on 20 cases before, during and after clinical death. The changes noted were sinus tachycardia, followed by sinus bradycardia and sinoauricular standstill; development of ectopic foci of irritability, resulting in nodal rhythm, single and multifocal ventricular premature contractions and ventricular paroxysmal tachycardia; appearance and disappearance of auricular activity; auriculoventricular block in various degrees; ventricular fibrillation; marked changes in the initial and terminal ventricular complexes; intraventricular conduction disturbances in various degrees up to bundle branch block. In many cases the electrocardiographic manifestations were noted as long as one hour after clinical death.

The factors responsible for these electrocardiographic changes appear to be disturbances in the vagosympathetic control of the heart, anoxemia, toxemia, and local nutritional and ionic disturbances in the heart. That anatomic disease of the heart itself is not responsible for the ultimate manifestations is evidenced from the fact that these changes occurred in the normal as well as in the diseased hearts. The sinus slowing and standstill, as well as the various grades of auriculoventricular block, appear to be mainly of vagal origin. Intraventricular disturbances depict changes in the distribution of the excitation waves and the order of excitation and retraction as well as transient focal blocking and localized partial or total refractoriness.

AUTHORS.

Kerr, J. D. Olav: Heart-Block in Coronary Thrombosis. Lancet 2: 1066, 1937.

Some degree of heart block is an occasional complication of cardiac infarction (coronary thrombosis) and its incidence, reckoning from 1,436 published cases of cardiac infarction, is 7.4 per cent.

A series of 13 cases is analyzed in which heart block first appeared under observation during the clinical course of coronary thrombosis. Of these, 4 had the slight degree of a prolonged P-R interval, 4 had partial, and 5 complete heart block. Seven of the 13, comprising all of the first group, 1 from the second, and 2 from the third group made good clinical recoveries, with disappearance of the block. Of the group with partial heart block, 2 died within a few weeks, and 1 was untraced. The

3 remaining patients with complete heart block died: 1 in an Adams-Stokes attack a week after the onset, the other 2 six weeks and eighteen months after the onset. Necropsies were performed in 2 of the 5 fatal cases, and the post-mortem reports are summarized.

Coronary thrombosis has to be included among the causes of chronic heart block seen either on account of bradycardia or clinical symptoms with or without Adams-Stokes attacks. In any collected series of cases of clinical heart block, those of acute onset from this cause should be separately considered.

The conductive tissues may escape completely in an extensive cardiac infarction while a localized occlusion of the vessels supplying the node and bundle may occur, creating too slight a disturbance to be recognized clinically as a cardiac infarction, though sufficient to produce heart block.

Although the prognosis of coronary thrombosis in general is adversely affected by the complication of heart block, clinical recovery and disappearance of the block is by no means uncommon.

AUTHOR.

Evans, William: Vitamin C in Heart Failure. Lancet 1: 308, 1938.

When compared with recognized diuretics, vitamin C was found to be as efficient as ammonium chloride in producing diuresis during one observation period but less efficient during two other periods. It was more efficient than theobromine during one trial period and less during another. In one patient it was less efficient than diuretin. It proved to be as efficient as digitalis in increasing the urinary output during one period of observation and more efficient during six others.

When a quantitative estimate was made of the excess of urinary output over fluid intake in the 9 patients over a period of 173 days, it was found that vitamin C induced greater diuresis than digitalis but less than theobromine, diuretin, and ammonium chloride. In each of 3 patients in whom heart failure had occurred with auricular fibrillation, vitamin C induced diuresis actually in excess of that produced by digitalis although never with the same degree of clinical improvement nor with reduction of the ventricular rate.

These results, attributing to vitamin C a diuretic property, direct attention to the need of providing an adequate supply of vitamin C for all patients with heart failure. In order to ensure a constant state of vitamin C saturation in heart failure it is probably enough to include in the patient's diminished fluid intake an adequate proportion of lemon and orange juice.

AUTHOR.

Evans, William: Early Diagnosis and Treatment of Heart Failure. Brit. M. J. 1: 1145, 1937.

In the diagnosis and prevention of heart failure it is important to seek early evidence of this in patients presenting heart disease which can ultimately precipitate failure, and in treatment it is necessary to individualize, to treat with determination but not overzealously, to prescribe remedies whose worth has been established by repeated and controlled clinical trial, to gain the full cooperation of the patient, and to give constant encouragement.

AUTHOR.

Courville, Cyril, and Mason, Verne R.: The Heart in Acromegaly. Arch. Int. Med. 61: 704, 1938.

This report is based on the observations of twenty-four patients with acromegaly. Of this group, eighteen (75 per cent) presented evidence of marked heart

failure, and six have died of heart failure. These six patients all had marked splanchnomegaly and cardiomegaly, and an eosinophilic pituitary adenoma was observed post mortem.

AUTHOR.

Silberberg, Martin: The Causes and Mechanism of Thrombosis. Physiol. Rev. 18: 197, 1938.

It has not been proved that the vascular endothelia have coagulative or anticoagulative properties of a specific kind or that the formation of a fibrin membrane on the vessel wall is generally the primary cause of thrombosis. Thrombosis occurs when the equilibrium of the factors on which the preservation of the ectoplasmic layer of the blood cells or the liquid state of the blood plasma depends is seriously interfered with. These factors may be localized in the blood itself, in the vascular endothelium, or in the perivascular tissues. They may be of mechanical, chemical, or physicochemical nature; they may be of bacterial origin and may be accompanied by inflammatory phenomena. On the whole, the results of the more recent work on thrombosis, as on other biologic phenomena, accentuate the importance of biochemical or physicochemical factors, in contradistinction to the tendency of scientific thought during the second half of the past century, in which special emphasis was laid on mechanical principles.

MONTGOMERY.

Gibson, Stanley, and Clifton, Willie Mae: Congenital Heart Disease: A Clinical and Postmortem Study of One Hundred and Five Cases. Am. J. Dis. Child. 55: 761, 1938.

A review of 1,950 consecutive autopsies on children revealed 105 cases of congenital heart disease. The relative incidence of congenital heart disease was much greater in infants than in older children. Of the 105 cases, 65 were instances of arterial-venous shunt and 25 of venous-arterial shunt, and in 15 there was absence of shunt. Of the 65 instances of arterial-venous shunt, 23 were pure defect of the interauricular septum; 17 consisted of patent ductus arteriosus, 12 of defect of the interventricular septum, and 13 of combined lesions. Symptoms were late or absent. The only characteristic auscultatory finding was that obtained in cases of defect of the interventricular septum. A harsh systolic murmur over the precordium was heard in practically every case of this type. The rarity of the humming top murmur in cases of patent ductus was surprising.

The majority of the children who had permanent venous-arterial shunt presented one of two conditions: complete transposition of the great vessels or the tetralogy of Fallot. All were cyanotic; the span of life was brief in the majority, and all died a cardiac death.

Of the fifteen children whose cardiac lesion did not allow abnormal communication between the systemic and the pulmonary circulation, some were free of symptoms and signs, while others succumbed to heart failure.

Cardiac findings in the seven cases of mongolism showed a variety of anatomic lesions.

AUTHOR.

Rinehart, James F., Greenberg, Louis D., Olney, Mary, and Choy, Frank: Metabolism of Vitamin C in Rheumatoid Arthritis. Arch. Int. Med. 61: 552, 1938.

The cevitamic acid content of the blood plasma is practically uniformly low for patients with acute rheumatic fever if a significantly high increase in the

intake of vitamin C has not been made preceding the determination. Furthermore, the majority of patients convalescent from rheumatic fever or with inactive rheumatic fever also show low blood plasma values. This study is in accord with that of Abbasy, Hill, and Harris, which was based on urinary excretion of vitamin C. Observations are cited indicating that a fundamental fault in metabolism of vitamin C exists in some cases of acute rheumatic fever. These data indicate that vitamin C deficiency commonly exists in rheumatic fever, and they add support to the concept that this deficiency may be of etiologic significance in the disease. Prolonged and carefully controlled prophylactic and therapeutic studies are indicated.

AUTHOR.

Boone, John A., and Levine, Samuel A.: The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency." Am. J. M. Sc. 195: 764, 1938.

From an analysis of 225 cases of "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed for an average of 9.6 years the following conclusions were drawn:

Of those cases diagnosed "potential rheumatic heart disease," 4.8 per cent subsequently developed mitral stenosis, aortic insufficiency or both. With a history of only a single attack of rheumatic fever or chorea, these patients had a 96 per cent chance of escaping valvular disease during five years after the attack, and 100 per cent after five years. With a history of repeated attacks, the chances were 94 per cent if less than ten years had elapsed since the first attack and 100 per cent after ten years.

Of those cases diagnosed "mitral insufficiency," 58 per cent persisted unchanged throughout the period of observation, while 42 per cent subsequently developed mitral stenosis or aortic insufficiency. Those with a history of a single attack of rheumatic fever or chorea had an 81 per cent chance of escaping further lesions before the lapse of five years, and 100 per cent after five years. With a history of repeated attacks their chances were only 39 per cent if less than five years had elapsed since the first attack, with a progressively more favorable prognosis as further years passed without the development of other lesions.

The occurrence of both rheumatic fever and chorea in the history was followed by a much higher incidence of valvular damage than following either disease alone, while that from rheumatic fever alone was about equal to that from repeated chorea alone. There were no instances of valvular disease following a single attack of chorea.

Some support was found for the theory that the greater tendency of chorea to produce mitral stenosis and the higher incidence of chorea in females is the explanation of the more frequent occurrence of mitral stenosis in females than in males.

AUTHOR.

Clark, Eliot R.: Arterio-venous Anastomoses. Physiol. Rev. 18: 229, 1938.

This is a brief survey of a very large body of literature on the anatomy of the minute arteriovenous anastomoses that normally occur in parts of the body of man and of animals. Concerning the function of arteriovenous anastomoses, the most one can say definitely is that, when dilated, they permit a large amount of blood to pass from artery to vein without passing through the capillaries. They undoubtedly play a part in the surface heating or cooling of the blood in the human hand and forearm. Other possibilities of function are only alluded to. With the definite establishment of their normal existence in certain regions, and with only a beginning made regarding their behavior in normal pathologic conditions, many problems press for solution.

MONTGOMERY.

Thomson, A. P.: Thrombosis of the Peripheral Veins in Visceral Cancer. Clin. J. 67: 137, 1938.

The author states that there is a much higher incidence of peripheral venous thrombosis in patients with cancer; so much so as to make the appearance of thrombosis of significance in differential diagnosis of cancer. This opinion has precedent (Trousseau, 1862), but the fact seems to have been forgotten. He reports three illustrative cases. In only one was the presence of cancer definitely demonstrated. The cause is not pressure (Trousseau's "Autopsy Studies").

MONTGOMERY.

Khoo, F. Y.: Calcification in Angiomata. Chinese M. J. 53: 127, 1938.

Seven cases of angioma with calcification are reported, special attention being paid to the roentgenologic aspect. This condition is not uncommon, the incidence being about 2 to 3 per cent of all cases of angioma. The calcified areas, or "phleboliths," vary in size from pinpoints to over 1 cm. in diameter.

MONTGOMERY.

Veal, J. Ross, and Van Werden, Benjamin De Kalb: The Physiologic Basis for Ligation of the Great Saphenous Vein in the Treatment of Varicose Veins. Am. J. Surg. 40: 426, 1938.

The direction of blood flow in varicosed great saphenous veins was observed by means of fluoroscopy after injection of thorium dioxide into the vein. In all parts of a varicosed great saphenous vein the flow is toward the foot. The radiopaque substance leaves the vein by way of deep communications within about 1½ to 7 minutes. After the great saphenous vein is ligated the blood leaves it much more slowly, and the flow in the upper segment of the vein ceases entirely. After ligation, the pressure within the great saphenous vein is the same, level for level, as before ligation. Hence, pressure changes play no part in the beneficial results obtained by ligation of the saphenous vein.

The treatment of a varicosed great saphenous vein consists of ligation of it and of its tributaries at its connection with the femoral vein, followed by repeated injections of a sclerosing solution into the saphenous vein. The upper segment (above the knee) is injected first, and thrombosed. Subsequent injections are carried out at weekly intervals and are best performed by making use of an elastic bandage in the following manner: An elastic bandage from foot to knee is lowered 4 to 6 inches per injection, the weekly injection being made just above the level of the bandage. The result of each injection is usually a firm clot in each segment of the vein thus exposed and injected.

MONTGOMERY.

Wilens, S. L., and Sproul, E. E.: Spontaneous Cardiovascular Disease in the Rat: II. Lesions in the Vascular System. Am. J. Pathol. 14: 201, 1938.

The manifestations of vascular disease in 487 rats of all ages in which death occurred as the result of natural causes are described. Only the coronary and pulmonary arteries were commonly the seat of degenerative changes. In the pulmonary arteries the lesion was frequently associated with calcification. Calcification was found also in other arteries, particularly the spermatic. A specific inflammatory disease of arteries identical with, or at least closely resembling, periarteritis nodosa in man was found in 9.7 per cent of the animals. Renal lesions similar to arteriosclerotic atrophy in the human kidney were described but their association

with vascular disease could not be established. The renal arterioles showed evidences of sclerotic changes in only a few exceptional cases, and in none was generalized arteriosclerosis recognized.

All of the lesions encountered were influenced by age, few of them being observed before the 700th day of life. Practically all of the change was in the media of the arteries. Internal lesions comparable to those in man and birds, in rabbits fed cholesterol, or in rats fed excessive doses of vitamin D were not found.

MONTGOMERY.

Krausse, L.: Experimental Investigation of the Action of Ultraviolet Light on the Arteriovenous Anastomoses. Ztschr. f. Kreislaufforsch. 30: 193, 1938.

Ultraviolet light opens up the arteriovenous anastomoses in rabbits. One-half hour irradiation causes the opening up of these communications after a latent period of four hours, and the maximum occurs in six to ten hours after the irradiation, at which time all the anastomoses appear open.

KATZ.

Petrén, T., and Sylvén, B.: Capillarization of Heart Muscle in Guinea Pigs. Morphol. Jahrb. 79: 200, 1937.

The distribution of capillaries in the heart of guinea pigs was determined in animals killed by histamine shock. The number of capillaries in the heart increase with the age of the fetus and continue to increase for three weeks after birth. The ratio of capillaries per square millimeter times the heart weight divided by body weight reaches a maximum at birth and decreases with postnatal age.

KATZ.

Scupham, George W., and de Tákats, Géza: Peripheral Vascular Diseases: A Review of Some of the Recent Literature and a Critical Review of the Surgical Treatment. Arch. Int. Med. 60: 522, 1937.

This introduces the annual review of an increasingly interesting and important branch of medicine. It is prepared similarly to one on heart disease. The review should be seen by everyone interested in the subject.

MCCULLOCH.

Rothschild, M. A., and Goldbloom, A. A.: Clinical Studies in Circulatory Adjustments: IV. Obliterating Pulmonary Arteritis With Secondary Pulmonary Changes and Right Ventricular Hypertrophy—Report of a Case With Autopsy. Arch. Int. Med. 61: 600, 1938.

There may be localized obliterating pulmonary arteritis without involvement of the other vessels, constituting a distinct clinical entity.

A case is reported in which this condition was diagnosed ante mortem and confirmed at autopsy.

Obliterating arteritis is differentiated from thromboangiitis obliterans in that the former is confined to the smallest arterioles without affecting the venous system.

The theory is advanced that the initial cause of the disease in our case was of an allergic nature. The condition began with anaphylactic shock, causing primary tachypnea with no dyspnea and resulting in interference with the pulmonary circulation. As the cause was not removed, there ensued secondary changes in the arterioles leading to obliterating arteritis, with consequent pathologic changes in the lungs. The right side of the heart became dilated as a result of enlargement of the right ventricle, producing anoxemia and abnormal electrocardiographic findings. Finally

the left ventricle, which could not receive a sufficient amount of blood, dilated, and there followed ventricular failure and pulmonary edema.

The clinical course of circulatory failure in our case bears a striking resemblance to the circulatory failure secondary to bronchial asthma, with permanent changes in the lungs, producing cardiac failure from overtaxation of the right side of the heart.

The finding of diminished oxygen saturation of the arterial blood is of diagnostic significance. Also indicative of pulmonary arterial obstruction, particularly in young persons, are cyanosis, tachypnea, with no orthopnea, and tachycardia.

This condition may be divided into three states: the immediate anaphylactic, the allergic and the terminal, with circulatory failure.

AUTHOR.

Stewart, Harold J., Deitrick, John E., and Crane, Normal F.: Studies of the Circulation in Patients Suffering From Spontaneous Myxedema. J. Clin. Investigation 17: 237, 1938.

In the presence of myxedema the cardiac output per minute and per beat are diminished, the velocity of blood flow is slow, and the heart larger than normal for that individual at a time when the basal metabolic rate is low. Moreover, the work per beat is low and not commensurate with the size of the heart. With the administration of thyroid extract and the increase of the basal metabolic rate to normal levels, the cardiac output increases per minute and per beat. The velocity of the blood flow increases, and the heart becomes smaller. The situation is then a reversible one. In the myxedematous state the arteriovenous oxygen difference is increased. There is present apparently a defect in the maintenance of the circulation since the circulation rate is slowed to such an extent that it is inadequate even to the decreased tissue requirements for oxygen. It has to be met by encroachment upon the arteriovenous oxygen difference. The explanation of this phenomenon is not now at hand, but it has been discussed in the light of Boothby and Rynearson's hypothesis with respect to hyperthyroidism. It has been demonstrated that the lengthening of the circulation time in myxedema bears a linear relationship to the cardiac output per minute as well as to the oxygen consumption; that the arteriovenous oxygen difference has a linear relationship to the oxygen consumption and the basal metabolic rate.

AUTHOR.

Montgomery, Hugh, Holling, Herbert E., and Friedland, Carl K.: The Effect of Iontophoresis With Acetyl-beta-methylcholine Chloride on the Rate of Peripheral Blood Flow. Am. J. M. Sc. 195: 794, 1938.

Numerous measurements of blood flow in the hands before, during, and after acetyl-β-methylcholine chloride iontophoresis were made in human subjects. There was consistently a great increase in blood flow.

Blood flow in the affected hands of three patients with obliterative disease of the arteries was greatly increased by acetyl-β-methylcholine chloride iontophoresis. There was some lasting effect in these patients as well as in normal subjects.

Systemic effects of the drug were rare. In the *untreated* hand there was no increase in blood flow. Current alone produced a slight increase in flow. Acetyl-β-methylcholine chloride without current did not alter blood flow.

In the two subjects studied, acetyl-β-methylcholine chloride iontophoresis increased peripheral blood flow to about the same extent as did reflex vasodilatation. The effect by iontophoresis was more lasting. The therapeutic possibilities of reflex vasodilation have not been tested.

In dogs systemic rather than local effects of the drug predominated. Whether this is a species difference or is related to the difference in experimental conditions is not known. The systemic effect varies with the concentraiton of the drug and the strength of the current, but is independent of the size of the electrode within the range of sizes used. In anesthetized dogs there was usually a mild, generalized increase in peripheral blood flow during acetyl-β-methylcholine chloride iontophoresis.

AUTHOR.

Heupke, W.: Fruit Diet in Heart Disease. Ztschr. f. Kreislaufforsch. 30: 257, 1938.

A diet consisting of 400 gm. of apples, 700 gm. of pears and 400 gm. of bananas compares favorably as regards calories and mineral content with the 1,000 gm. of milk (Karell diet). The author advocates a fruit diet in congestive heart failure.

KATZ.

Starr, Isaac, Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, N., and Eagle, E.: A Clinical Study of the Action of 10 Commonly Used Drugs on Cardiac Output, Work, and Size; on Respiration, on Metabolic Rate, and on the Electrocardiogram. J. Clin. Investigation 16: 799, 1937.

The subjects consisted of 85 patients suffering chiefly from cardiac or circulatory disease but not from congestive heart failure. The number of patients tested for the effects of each drug varied from 2 to 16.

The drugs investigated included digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerin, pitressin, quinidine, morphine, and strychnine. As far as possible, we studied the action of drugs given under the conditions in which physicians are accustomed to employ them.

The study consisted of a group of estimations made before, during, and sometimes after the drugs' action. This group consisted of duplicate determinations of cardiac output and metabolic rate; and repeated estimations of pulse rate, blood pressure, and respiratory rate and volume. Orthodiagrams and electrocardiograms were secured also.

Based on a conception derived by Starling and his associates from the behavior of the dog's heart-lung preparation, a method has been devised for estimating the extent of myocardial stimulation or depression occurring during drug action in the clinic.

A statistical analysis of the data affords a basis for describing the action to be expected after the administration of these drugs in clinical conditions. With but few exceptions our results support the general conceptions of drug action derived from animal experiments.

The tables contain data on the basal cardiac output and its related functions in many common diseases of the heart and circulation.

AUTHOR.

Book Reviews

HEART DISEASE IN GENERAL PRACTICE. By Paul D. White, M.D., Lecturer in Medicine, Harvard University Medical School. New York, 1937, National Medical Book Company, Inc.

The heyday of the all-inclusive text on every subject has passed. Handbooks such as this, based upon the essential facts and written by men of wide experience, are the order of the day. Dr. White's book will be welcomed both by the general practitioner and the internist, for it summarizes his broad experience and epitomizes his comprehensive work, "Heart Disease," which is the source book of cardiology in this country.

In this handbook Dr. White has used the method of question and answer which he has found most successful in his postgraduate teaching. This style may not appeal to everyone, for it is not as easy to follow as an outline form in which the main point of each question is used as a heading. There is a great deal of information in the simple, clear paragraphs. Some dogmatism is inescapable in a book such as this, but there are very few statements which one might question. In his succinct answers the author usually imparts wisdom and understanding, as well as the facts. Most of the significant and practical aspects of cardiac diagnosis and therapy have been touched upon. The facts necessary for the solution of any given problem are easily available, and frequently the author's statements are augmented with observations which will be of future use to the clinician. By stripping his subject of much of its complexity, he makes it more interesting and encourages further study.

Brevity is the keynote, but it has not been carried to extremes. The first part of the book is devoted to history taking and the next to methods of examination. These are followed by a chapter on prognosis and treatment, and a useful appendix dealing with cardiovascular emergencies.

The book is recommended without reservations to the practitioner and the internist who require a brief, practical survey of the entire field.

GEORGE HERRMANN.

DIE IRRADIATION AUTONOMER REFLEXE—UNTERSUCHUNGEN ZUR FUNKTION DES AUTONOMEN NERVENSYSTEMS (THE SPREAD OF THE AUTONOMIC REFLEXES—INVESTIGATIONS ON THE FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM). By Dr. Alfred Schweitzer. Basel, Switzerland, 1937, S. Karger, 375 pages, 38 illustrations.

This monograph deals with the phenomena of spread of reflexes in the autonomic nervous system. It is based on an extensive review of the literature and the work of the author in this field. The point is made that the autonomic nervous system shows as much integration as does the nervous system controlling the skeletal muscles. The impulses for this integration arise in part from the sense organs located in the skin, subcutaneous tissues and in muscle and joints, as well as those from the ear, eye, and labyrinth. These sense organs are almost as important in integrating the activities of visceral functions as are those located in the respiratory tract, gastrointestinal tube and circulatory tree. The picture is painted of a

beautiful correlation of the vascular, respiratory, and gastrointestinal systems by means of this integrated nerve action. The importance of this coordinated nervous activity in health and disease is stressed. This monograph is particularly stimulating because it emphasizes that visceral coordination is not confined alone to impulses arising from the carotid sinuses and aortic sensory areas as has been stressed so much recently, but is the result of nervous impulses coming from other visceral sense organs as well as general and special somatic sense organs. It serves the useful function also of amplifying the concept of homeostasis as it affects the autonomic nervous system. Of particular interest to cardiologists is the part in this coordination carried out through the cardiovascular system. A minor criticism of this monograph is that the author probably overemphasizes the importance of this integration in relation to humoral homeostasis. An extensive bibliography and excellent indexes are appended.

L. N. KATZ.

KLINIK UND THERAPIE DER HERZKRANKHEITEN UND DER GEFÄSSERKRANKUNGEN. Vorträge für praktische Ärzte. By Privatdozent Dr. D. Scherf, Wien. Ed. 4, Vienna, 1938, Julius Springer, 10 illustrations, 312 pages.

The appearance of four editions of this volume in a little over three years is evidence of its popularity. The original booklet consisted of lectures on the diagnosis and treatment of diseases of the heart and circulation which were given for postgraduate students in Vienna. With each revision, chapters were added and new material was incorporated.

The book is not a text; nor does it pretend to present exhaustively the topics discussed. No bibliography is given, no electrocardiograms are pictured, and there are only ten illustrations, but the subjects chosen for consideration are covered adequately, though briefly, from the point of view of the practicing physician. The clinical descriptions and therapeutic recommendations are based upon the author's own experience. It is evident that he is familiar with the views of others and has incorporated the best of these into his own well-considered opinions.

There are three main divisions. The first deals with general considerations, the second with diagnosis, and the third with treatment. In the first part are considered chiefly the symptoms and signs of myocardial insufficiency. Particular emphasis is placed upon the various types of dyspnea and the mechanisms concerned in their causation. In presenting the material for diagnosis, there is no attempt at systematic arrangement. Valvular diseases are classified anatomically rather than according to etiology. Hypertension and diseases of the aorta and myocardium are grouped together. There are, among others, sections on cor pulmonale, the heart in hyper- and hypothyroidism, the cardiac neuroses, endocarditis, syncope and the Adams-Stokes syndrome, pericarditis, congenital anomalies, and affections of the peripheral vessels. There is a short chapter on arrhythmias and an excellent discussion of angina pectoris. Under therapy appear discussions of digitalis, strophanthin, morphine, venesection, carbon dioxide baths, specific treatment of syphilitic aortitis, total thyroidectomy, diuretics and diet. Certain suggestions with regard to the use of drugs are not in accord with current opinion in this country. For example, administration of digitalis by rectum is not considered the method of choice. In general, however, the treatment outlined is sound and modern.

The book is written for the general practitioner rather than for the specialist in cardiology. The author has succeeded admirably in presenting in a clear and concise manner the essential clinical features and therapy of cardiovascular diseases.

ROBERT L. LEVY.

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Original Communications

EFFECT OF EXCESS SUGARS ON THE PERFUSED RABBIT HEART*

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ACTIVE controversy concerning the fuel of the heart has continued for several decades. Although dextrose was long considered the only or chief utilizable foodstuff,[4, 17] it was early appreciated[19] that the quantity actually consumed by the heart was only a few milligrams per gram of heart muscle per hour. Later, more critical investigations employing improved and refined methods of study eliminated or evaluated the appreciable glucose disappearance that results from bacterial decomposition,[3] from glycolysis in the blood,[8] and from oxidation in the lungs,[8, 22] and it is now believed that the heart uses probably only 0.2 or 0.3 mg., and possibly less than 0.1 mg., of glucose per gram of muscle per hour.[4, 7, 22]

In recent years lactic acid has gained increasing recognition in the energy metabolism of the heart,[6, 13, 22, 23] but dextrose is still regarded as a probably important accessory fuel, or perhaps even as the major precursor of the lactic acid.[8] Finally, dextrose appears favorably to influence the synthesis of phosphocreatine.[20, 26] It is thus evident that dextrose plays a significant if not a major role in this still insufficiently elucidated phase of cardiac metabolism.

In spite of the diversity of opinion from the physiologic laboratories concerning the actual fuel or fuels of the heart, their relative importance, and the precise role played by dextrose, there has been a growing clinical interest, evident particularly in the foreign literature, in the liberal parenteral administration of dextrose in acute and chronic heart failure.[14, 27, 29]

Since judgment of the efficacy of this sugar has been based almost entirely on clinical impression, and opinion has been conflicting,[22, 23] it

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was considered desirable to attempt a more objective study on animals in the laboratory. Abundant consideration has long been given to the metabolic aspects of heart muscle physiology.[4] Merely to demonstrate, however, that heart muscle may under certain conditions of fuel supply increase its oxidative metabolism does not necessarily indicate that the organ has become more efficient directly as a result of its greater consumption of a more generously provided foodstuff. The diseased, dilated, anoxic, or otherwise failing heart is perhaps a less efficient mechanism and may convert too little of its oxidative energy into useful work. Metabolic studies alone, therefore, are not adequate quantitative criteria of efficiency; observations of the organ's actual performance are essential.

As the first step in determining the influence of sugars on cardiac behavior we sought the simplest surviving heart preparation and chose primarily to observe the effect of excess concentrations of dextrose on two characteristic phenomena, namely, myocardial activity and coronary flow. These observations appeared most conveniently obtainable in the isolated and saline-perfused heart, which is free from external nervous, hormonal, or metabolic influence.

METHODS AND PROCEDURE

The apparatus we have devised (Fig. 1) was based on the Langendorff method of perfusion.[16] Several modifications were introduced to permit ready shifting from one perfusate to any of three others without significant change either in perfusion pressure or temperature. Provision was also made for perfusing with either oxygen-saturated or with oxygen-deficient solutions.

The source of perfusion pressure was a Marriott bottle, *A*, filled with tap water, and suspended from the ceiling. The perfusion pressure, as determined by the height of the Marriott stopper above the level of the coronary ostia, could be varied as desired; it was usually fixed around 70 cm. Water from *A* displaced either oxygen or nitrogen from the gas pressure reservoirs *B* and *C*, forcing the gases into the preheated perfusates in incubator *D*. These gases served both as the final source of pressure and as supplementary means of saturating the perfusates. The oxygen-deficient solutions were prepared by bubbling nitrogen long and freely through bottles of perfusate. The solutions were then forced through a system of individual glass coils suspended in an agitated water bath in electric oven *E*. The outflow from the four coils converged into a single short insulated tube leading to the aortic cannula.

The heart *H*, suspended by a U-shaped cannula in the aorta, was enclosed in the covered chamber *F*, the interior of which was kept warm and moist by water circulating outside of the funnel receiving the coronary outflow. The outflow from the heart represented the flow through the coronary system only, since the pulmonary veins were ligated. This was attained by ligating the pulmonary vessels en masse and opening the pulmonary artery; the venae cavae were left open. The coronary flow was collected in a Condon tip recorder *G*, adjusted to empty and record electrically each collection of approximately 3 c.c. The apex of the heart was steadied by a spring clip. A thread leading from the right ventricular wall to a muscle lever recorded the amplitude and rate of contractions. Inasmuch as no sudden changes in rate were encountered, an artificial pacemaker to control this factor

was not considered necessary. The temperature T of the perfusates was kept near 37.5° C. This temperature tended gradually to decline as the coronary outflow diminished in the course of a prolonged experiment, yet with any single shift from one solution to another a change of 0.2° C. was seldom introduced and only rarely exceeded.

Hearts obtained from rabbits, killed by a sudden blow on the occiput, were used throughout. The perfusion was always begun with normal Ringer-Locke solution

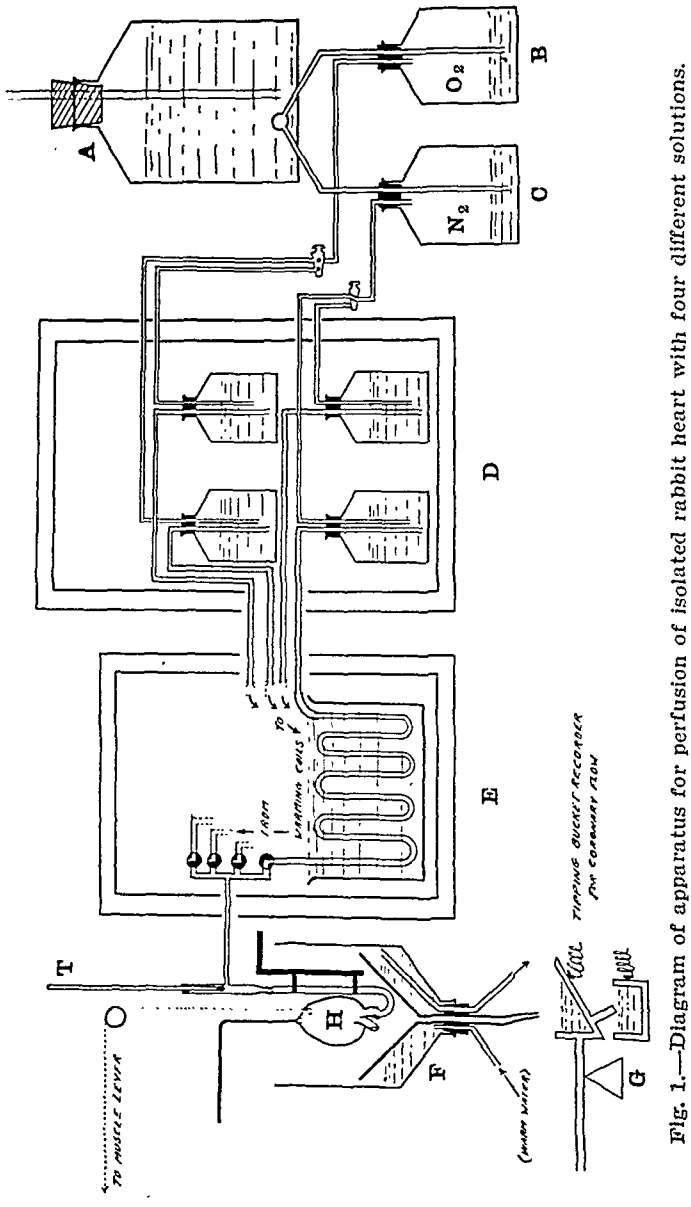

Fig. 1.—Diagram of apparatus for perfusion of isolated rabbit heart with four different solutions.

containing 0.1 per cent dextrose. Perfusion was continued for at least thirty minutes and until the action of the heart was uniform and satisfactory, after which the solutions under investigation were introduced. Ringer-Locke solution of nitrogen-ion concentration 8.0 to 8.4 was the basis for all the perfusates employed; the composition of the perfusate was sodium chloride 0.92 per cent, potassium chloride 0.042 per cent, calcium chloride 0.012 per cent, and sodium bicarbonate 0.03 per cent.

RESULTS

The results to be presented were in general consistent, regardless of whether the preparations were fresh and active or failing from prolonged perfusion. The final responsiveness of the seriously failing heart was usually proved at the end of an experiment by an injection of 0.3 mg. of epinephrine.

Hypertonic Dextrose Perfusates.—Nineteen hearts were perfused with Ringer-Locke solution to which excessive amounts of dextrose were added. The experiments were of two types. In one group of fifteen hearts a perfusate in which the dextrose content was raised to 1 per cent was selected as corresponding to the higher concentrations obtained clinically with intravenous dextrose therapy.[24, 32] In the other four experiments a perfusate made twice osmolar with 5.6 per cent dextrose was chosen primarily to observe the effect of hypertonicity. Control experiments employing equivalent concentrations of sucrose are described below.

With the 1 per cent dextrose perfusate a stimulating effect on the heart muscle was observed consistently in thirteen hearts, and no effect occurred in three hearts, including one in which an earlier positive effect was not reproducible. The coronary flow was increased in eleven of the fifteen hearts, and no response was obtained in seven hearts, including three which showed positive effects during another trial. Figs. 2, 3, 4, and 6 illustrate positive effects on the heart muscle obtained with the 1 per cent dextrose perfusate; and Figs. 2, 4, and 6 show increase in coronary flow preceding the increase in stroke amplitude.

When the 5.6 per cent dextrose perfusate was employed in four hearts, the myogram showed either no stimulation or actual depression in two hearts, stimulation in one heart, and inconsistent effects in another. The coronary flow was increased in four of the five hearts. Fig. 5 gives an example of both positive effects with the 5.6 per cent dextrose perfusate.

The observed "stimulating effect on the heart muscle" generally consisted of a gradual augmentation in the amplitude of the cardiac contractions, which usually began almost immediately on the introduction of the effective perfusate and persisted for several minutes; the amplitude then gradually declined again until it was approximately what it had been under the original control perfusate. Increases in coronary flow attributable to a change in perfusate always appeared promptly on the introduction of the perfusate; if effective, they lasted for from one to several minutes, after which the flow then usually declined moderately. The augmentation of the stroke amplitude was almost invariably preceded slightly but definitely by the increased coronary flow, and sometimes, as in Fig. 9, the coronary flow was increased even in hearts so feeble that no stimulation of the muscle was evident in the

myogram. These last observations are important, for they answer the criticism, at least for these cases, that the increased coronary flow might have been apparent only, not real, and due to the emptying of the right

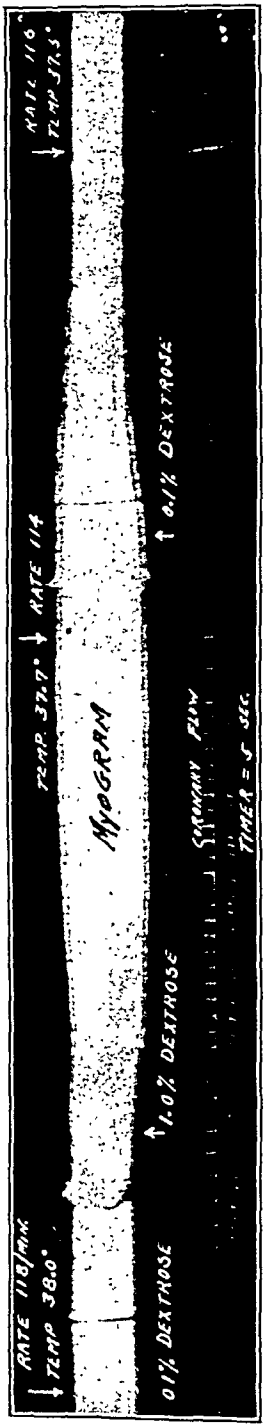

Fig. 2.—Rabbit heart. Typical positive effect of hypertonic dextrose perfusate on myogram and coronary flow.

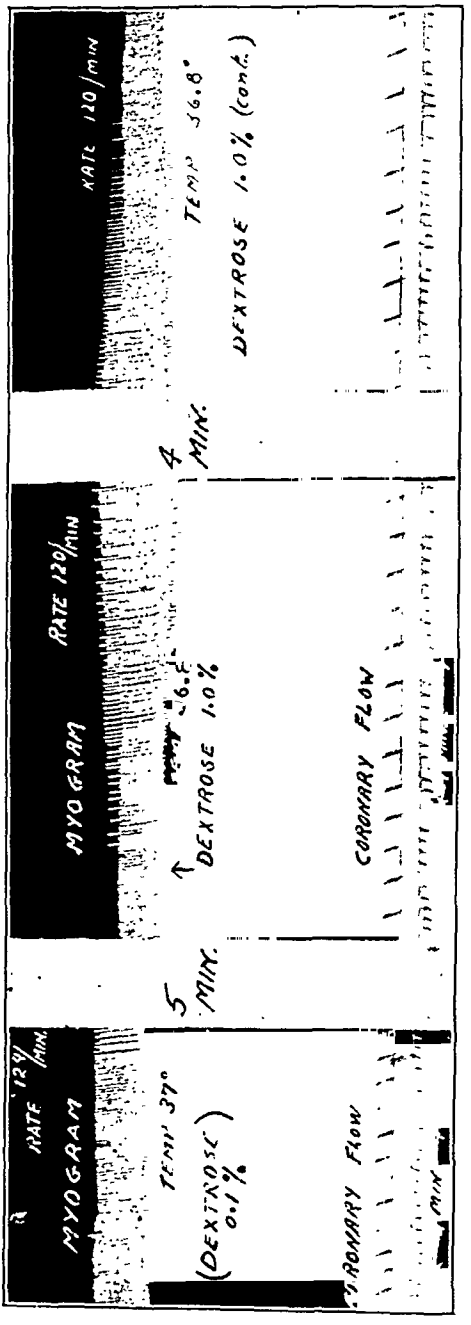

Fig. 3.—Rabbit heart. Positive effect of hypertonic dextrose perfusate on myogram. No effect on coronary flow.

ventricular cavity accompanying its increased vigor of contraction. Another error recognized as inherent in this method of recording coronary flow, but one which does not alter our interpretations, is the

leak past the aortic valves of perfusate which is added to that coming from the heart by way of the coronary vessels. Our interpretations concerning the coronary circulation, however, are based not on absolute values but on changes in flow; no significant changes in aortic leak would be expected with our uniformly maintained aortic pressures. Furthermore, changes in flow usually preceded any increased activity

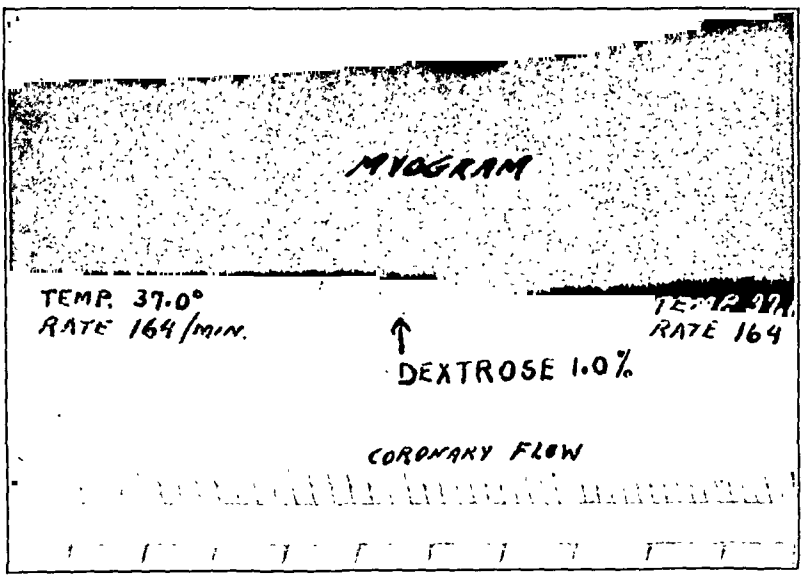

Fig. 4.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Change to 1 per cent dextrose results in increase in myogram and coronary flow.

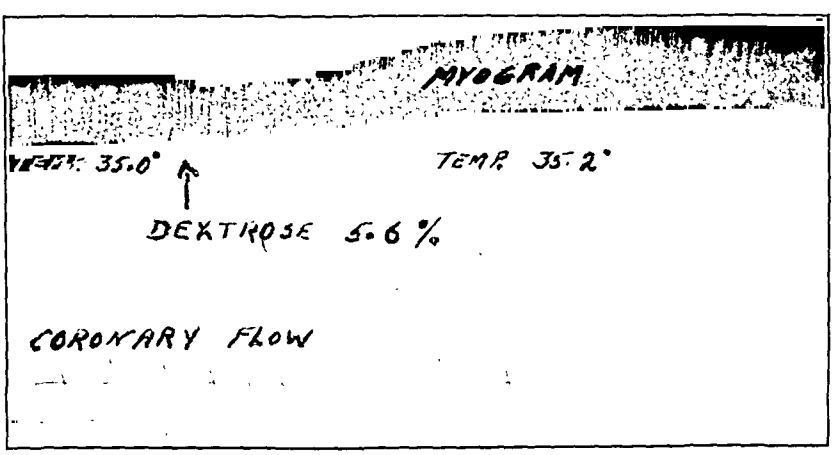

Fig. 5.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Changing to 5.6 per cent dextrose results in transient increase in myogram and coronary flow.

of the heart which might have disturbed the anatomic relationships of the aortic leaflets and altered the competency of the valves. Finally, augmentation of flow occasionally occurred without either simultaneous or subsequent stimulation of the muscle.

Hypertonic dextrose, therefore, appeared usually to increase the coronary flow, but muscular stimulation was more regularly evident only with the 1 per cent dextrose perfusate.

Each of two rabbits was given one intravenous injection of 50 mg. caffeine sodiobenzoate per kilo, followed in two minutes by 0.2 mg. epinephrine. This procedure is known to result constantly in myocarditis in rabbits.[9, 12, 15] Several weeks later these animals were sacrificed and the hearts perfused as above with isotonic and hypertonic

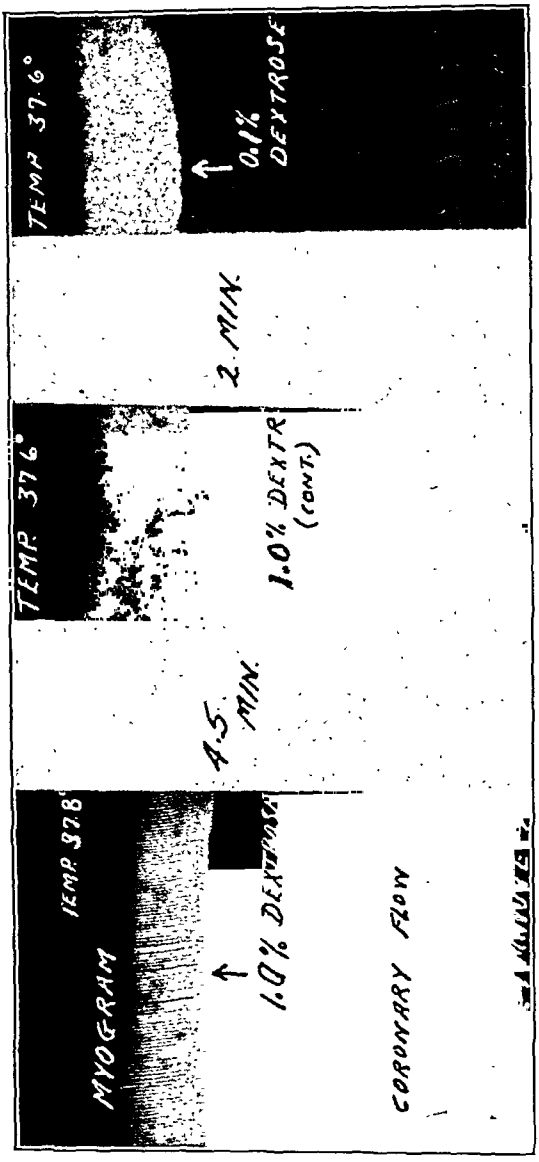

Fig. 6.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Changing to 1 per cent dextrose results in increased myogram and coronary flow.

dextrose solutions. Moderate increase of coronary flow and augmentation of the myogram indistinguishable from that already described with previously uninjured hearts were observed with the 1 per cent dextrose perfusate. The injured hearts showed pericardial adhesions and gross scarring of the myocardium.

That the heart may not accumulate a significant fuel reserve when generously supplied with an excess of dextrose is evident from Fig. 7.

This heart had been perfused for fifty minutes with a Ringer-Locke solution containing 1 per cent dextrose, yet on changing to a dextrose-free perfusate progressive failure promptly set in.

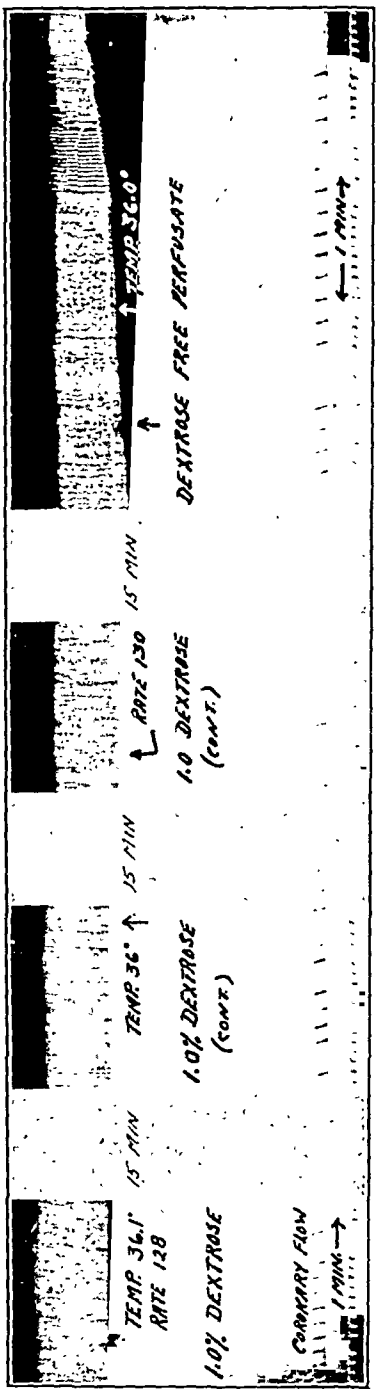

Fig. 7.—Rabbit heart. Perfusion with hypertonic dextrose for fifty minutes is followed by rapid failure of contraction when a dextrose-free perfusate is introduced.

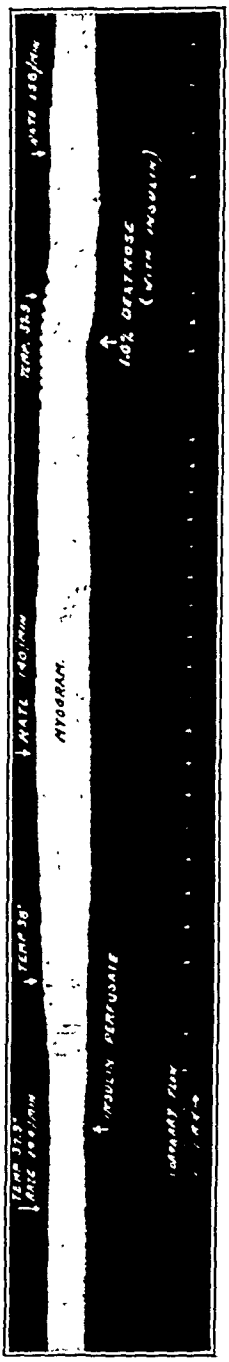

Fig. 8.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. Introduction of insulin-containing perfusate is followed by sustained augmentation of myogram, with slight further stimulation when 1.0 per cent dextrose replaces 0.1 per cent dextrose perfusate.

To observe the effect of excess dextrose in the presence of insulin, this hormone was injected into the perfusing cannula in several experiments, and in two other experiments 100 units of insulin were mixed with each liter of perfusate. The simple injection of insulin into the perfusing

cannula was apparently without effect with either the 0.1 per cent or the 1 per cent perfusates. The mixture of the insulin and the perfusate containing 0.1 per cent dextrose caused no increase in heart rate, but was followed by a moderate and fairly sustained increase in the stroke amplitude and the coronary flow in one experiment (Fig. 8); there were no significant effects in another experiment. In accord with these obser-

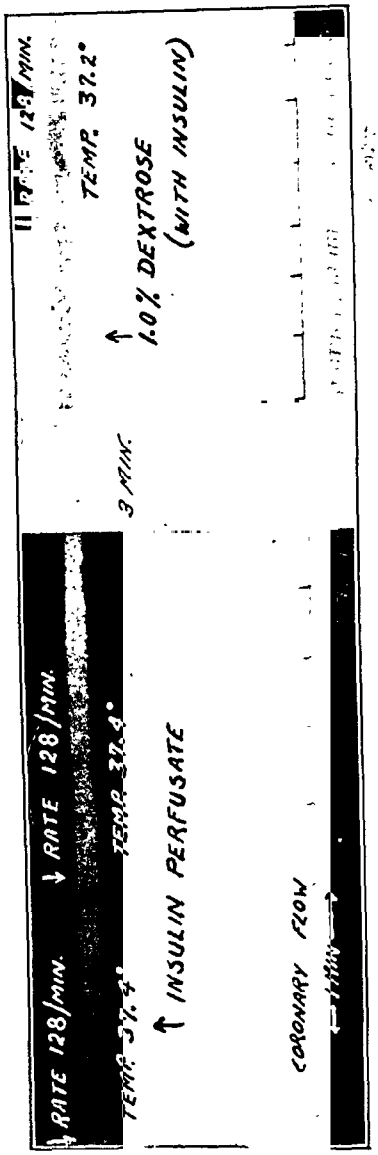

Fig. 9.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose. No effect on myogram or coronary flow with either added insulin or excess dextrose.

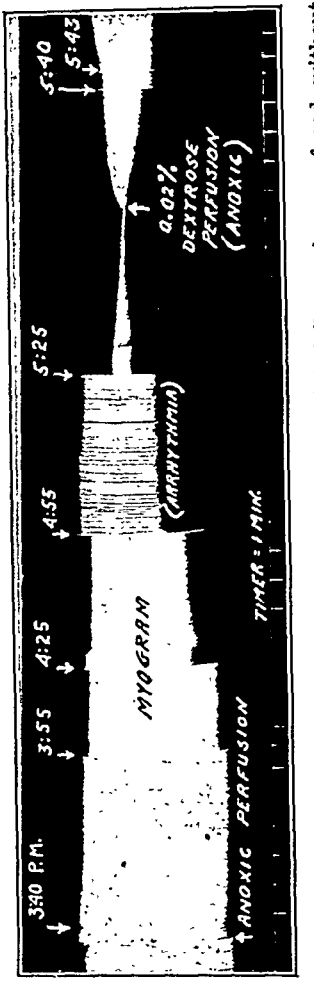

Fig. 10.—Frog heart. Shows gradual myocardial failure when perfused without oxygen and without carbohydrate. Prompt recovery of activity under continued anoxic conditions when dextrose is introduced.

vations are those of Bodo,[2] who observed a prolonged increase in cardiac tone in the heart-lung preparation when insulin was injected. When we introduced a 1 per cent dextrose solution along with the insulin perfusate in one experiment there followed a slight increase in the stroke amplitude but a diminution of coronary flow (Fig. 8); in a second experiment the admission either of insulin or of 1 per cent dextrose had no apparent effects (Fig. 9).

It appears from one of two experiments that insulin itself may on occasion slightly augment the coronary flow and stroke amplitude of the perfused rabbit heart. However, neither the myogram nor the coronary flow gives evidence of any greater benefits from excess dextrose when insulin is present in the perfusate.

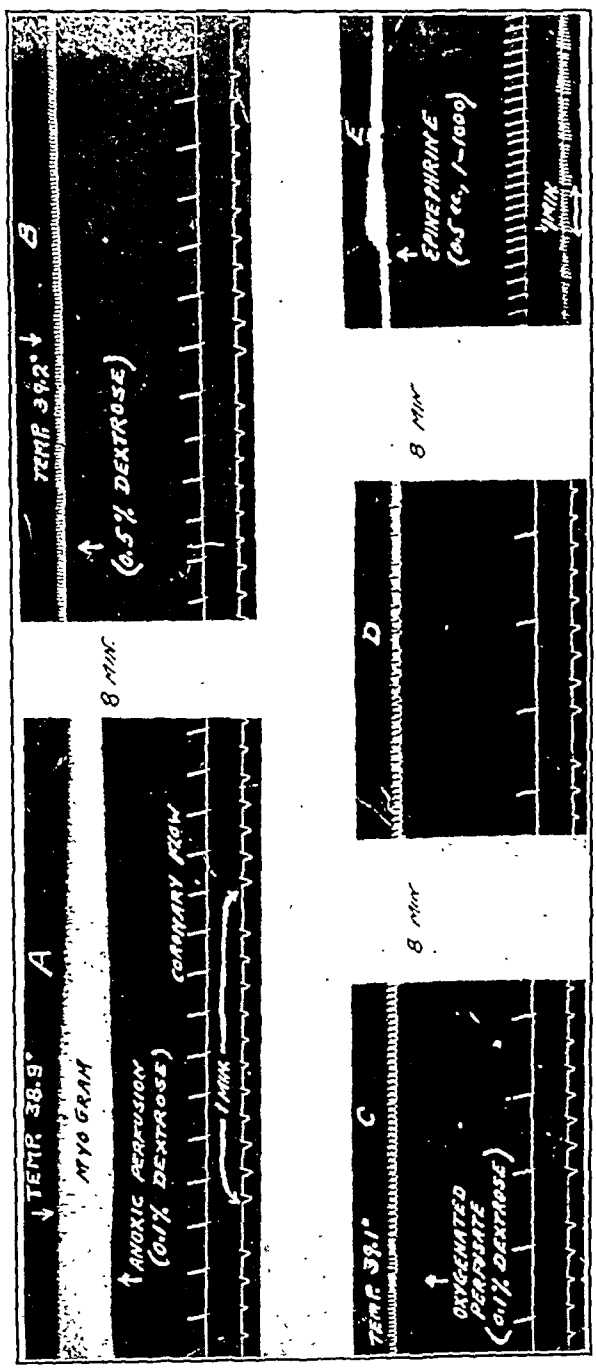

Fig. 11.—Rabbit heart. (Eight-minute intervals between segments.) *A.* Failure of myogram with anoxic perfusion. *B.* No beneficial effect from hypertonic dextrose perfusate. *C and D.* Tendency toward recovery on readmission of oxygenated perfusate. *E.* Myocardium still capable of being stimulated by epinephrine.

Oxygen-Deficient Hypertonic Dextrose Perfusates.—Freund and König[10] observed complete and sustained cessation of activity in the isolated frog heart when perfused in an atmosphere of nitrogen with

an alkaline Ringer solution free from oxygen and dextrose. The addition of dextrose alone to the perfusate produced dramatic resumption of rhythmic contractions. This effect we readily confirmed in each of two intact frog hearts kept in an atmosphere of nitrogen and

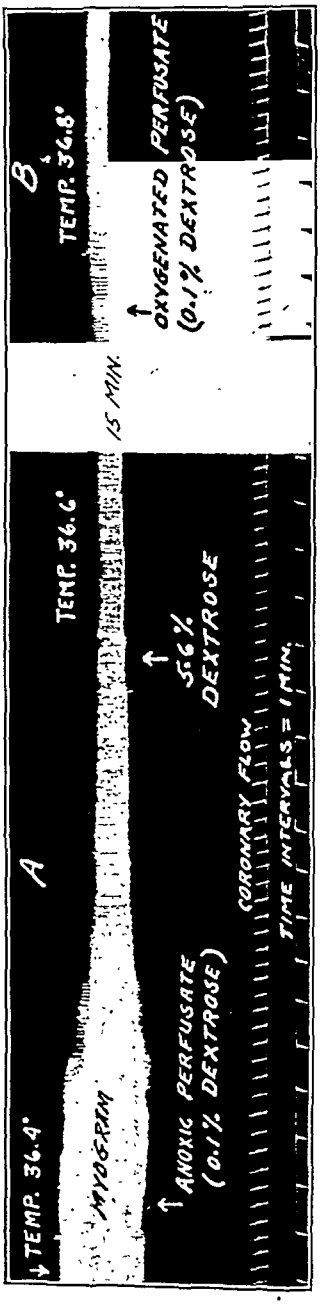

Fig. 12.—Rabbit heart. *A*, Decline of myogram under anoxic perfusion without improvement with hypertonic dextrose. *B*, Tendency toward recovery on readmission of oxygenated perfusate.

perfused through the postcaval veins after the method of Sollmann and Barlow.[28] The perfusate employed was Howell's frog heart Ringer solution brought to nitrogen-ion concentration 8.2 with 0.05 per cent sodium bicarbonate. Fig. 10 depicts the anoxic failure of the frog heart and its prompt revival with dextrose.

Pollack and Wilder,[26] working with dogs, argued that anoxemia caused a breakdown of the phosphocreatine mechanism as a source of energy, offering this in explanation of the damaging effect of anoxemia in heart disease. Their observation that the intravenous administration of glucose is followed by a fall in the serum phosphates and their deposition in skeletal and cardiac muscle led them to the conclusion that glucose, through its synthesizing action on phosphocreatine, can to a certain extent overweigh or overbalance the hydrolyzing effect of anoxemia on phosphocreatine.

The above indications that the metabolism of the heart muscle may be fundamentally altered in anoxemia led to the following experiments with oxygen-deficient perfusates:

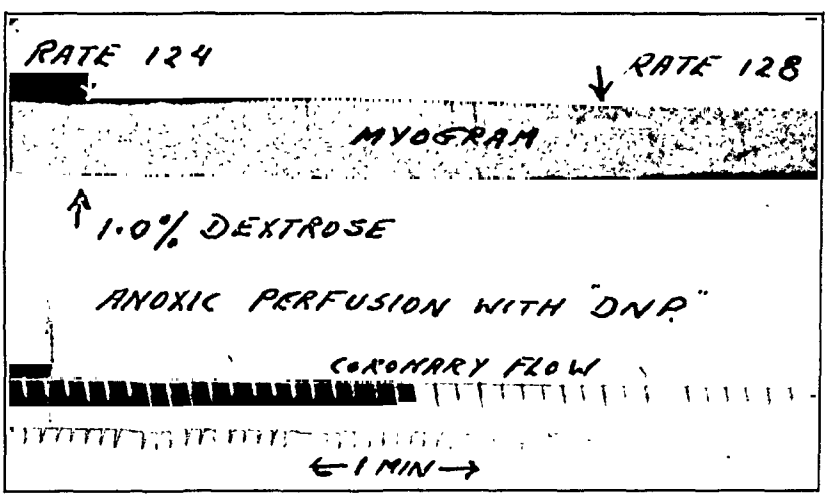

Fig. 13.—Rabbit heart. Perfusion begun with oxygen-free 0.1 per cent dextrose solution. Slight augmentation of myogram on changing to 1 per cent dextrose.

After normal and uniform activity had become established in the excised and perfused rabbit heart, an oxygen-deficient Ringer-Locke solution was introduced. Slow and gradual failure followed in each of the seven hearts so treated; a typical example of this effect is illustrated by Fig. 11. To accelerate this failure, for purposes of convenience, alpha-dinitrophenol (1:20 million dilution) was added to the perfusate in five additional experiments. This concentration had been found to stimulate the activity of the heart without apparent injury.[11] The administration of 1 per cent dextrose was followed by a transient stimulation of muscular contraction, or a temporary retardation of previous gradual failure in six out of ten such failing hearts. The coronary flow in these experiments was increased, decreased, and unaltered in about equal numbers. Fig. 12 depicts simple anoxic failure without evident benefit from excess dextrose, and Fig. 13 illustrates a slight improvement with 1 per cent dextrose in anoxic failure accelerated by alpha-dinitrophenol.

If the asphyxial depression of the rabbit heart was permitted to proceed to complete cessation of activity, no revival could be accomplished by the administration of dextrose, as in the case of the frog heart.

Apparently the introduction of hypertonic dextrose perfusates under anoxic conditions caused only such changes in mechanical activity of the heart and alterations in coronary flow as had already been observed under conditions of adequate oxygenation. It must be remembered, in applying our results to the conclusions of Pollack and Wilder,[26] that our perfusates were the Ringer-Locke solution, and were lacking in utilizable phosphates.

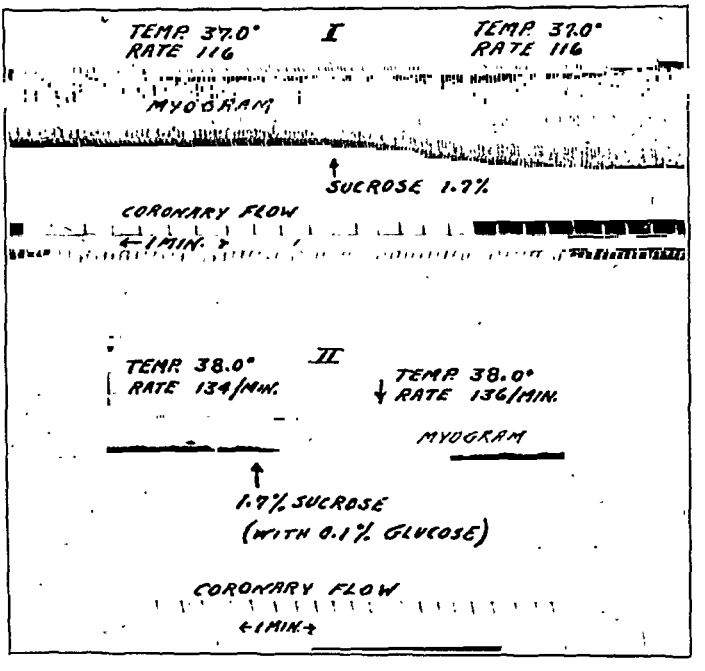

Fig. 14.—Rabbit hearts. Perfusion begun with 0.1 per cent dextrose solution. Both experiments show augmentation of myogram and coronary flow on addition of 1.7 per cent sucrose.

Sucrose Perfusates.—To determine whether the results obtained with dextrose were metabolic or osmotic in character, control observations were made with the nonutilizable sugar, sucrose. Sucrose was added to the Ringer-Locke solution, which contained the usual 0.1 per cent dextrose, in two concentrations corresponding to the two concentrations of excess dextrose employed in previous experiments, namely, 1.7 per cent and 10.4 per cent sucrose, osmotically equivalent to 0.9 per cent and 5.5 per cent dextrose respectively.

In the course of any single experiment the corresponding sucrose and dextrose perfusates were always compared. In seven hearts studied in this manner the results on muscular contraction were about equally divided between augmentation and no effect, both for the higher and the lower concentrations of sucrose. The coronary flow, however, was

definitely increased by the higher concentration of sucrose in each of three hearts, and with the lower concentration an increased flow resulted in three out of four hearts. Fig. 14 shows two experiments in which the introduction of a hypertonic sucrose perfusate resulted in augmentation of the stroke amplitude and slight increase in coronary flow. Fig. 15 illustrates the essential similarity of effects from either dextrose or

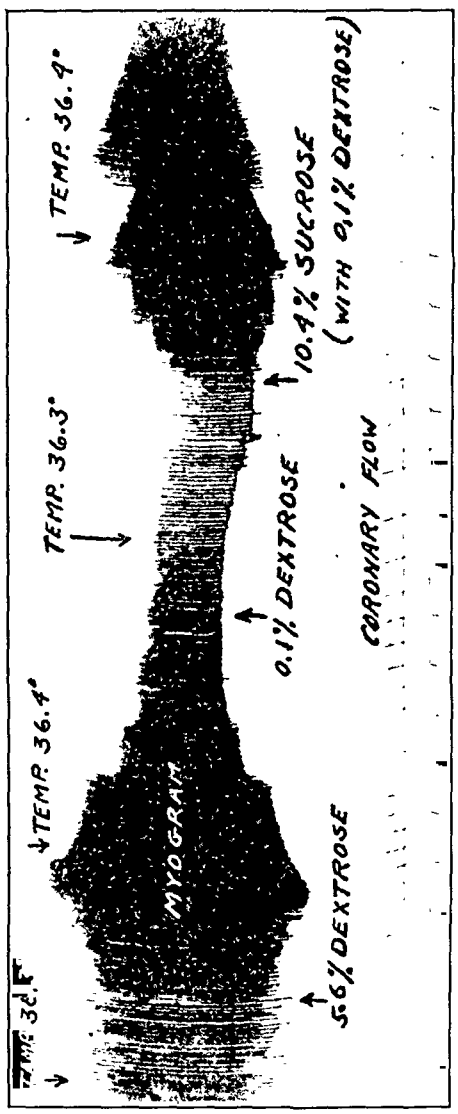

Fig. 15.—Rabbit heart. Perfusion begun with 0.1 per cent dextrose with transient stimulation of myogram and coronary flow under 5.6 per cent dextrose and later a similar response to an equivalent concentration of sucrose.

sucrose in excess concentrations. In general, then, the results with sucrose are seen to be similar to those obtained with dextrose concentrations of equal tonicity.

It is re-emphasized that in all the preceding experiments with sucrose the perfusates always contained 0.1 per cent dextrose also. One heart, however, was perfused with dextrose-free Ringer-Locke solution containing 0.1 per cent sucrose, and the anticipated prompt failure was noted.

DISCUSSION

Although some variation of results was obtained in these experiments, such inconsistencies are not unexpected under the relatively unphysiologic conditions surrounding the perfused isolated heart. On the basis of a reasonably large number of experiments, however, it seems permissible to venture certain conclusions concerning the myocardial and coronary effects of sugars furnished in excess concentrations.

The old observation that dextrose is an acceptable ingredient of a perfusate for the heart was again simply confirmed by these experiments. A small quantity of this sugar in a perfusate suffices to sustain contraction of the heart. Sucrose, however, failed as a fuel substitute for dextrose, as Maclean and Smedley observed in 1913.[21]

But acknowledgment that dextrose has definite value as a cardiac fuel need not imply that its excessively liberal administration will increase utilization, storage, or work. In fact, previous investigators have already suggested a negative answer to this question. Cruickshank and Startup[5] found only a 10.5 per cent increase in sugar oxidation in the heart-lung preparation in the presence of hyperglycemia, and the increased oxidation was not in proportion to the degree of hyperglycemia. Furthermore, since it is now apparently established[4, 6] that the heart utilizes only a fraction of a milligram of dextrose per gram of muscle per hour, it seems entirely reasonable that the sugar content of the blood and the abundant stores in the muscles, skin, and other tissues are in themselves ample to meet even a great increase in the oxidative capacity of the heart. Finally, Starling and Visscher[30] found that although the failing heart may utilize as much oxygen and liberate fully as much energy at any fiber length as the normal heart, the failing organ converts much less of this energy into work; in other words, the efficiency of the failing heart is definitely lower. It seems a logical conclusion, therefore, that the essential need of the failing heart does not lie in its demand for greater quantities of fuel.

Whether or not insulin appreciably increases the glucose utilization of the heart is still disputed.[4] Visscher and Müller[31] found no evidence that insulin had any direct stimulatory effect on the oxidative metabolism of the isolated heart. Insulin apparently did not increase the rate of disappearance of sugar from the heart-lung preparation in Plattner's experiments,[25] and Cruickshank and Startup,[5] in similar preparations, found that the addition of insulin resulted in only a 3.6 per cent increase in sugar oxidation even in the presence of hyperglycemia. Our experiments support the view that the addition of insulin to the excess of dextrose does not augment in any significant manner the effects obtained with dextrose alone.

Inasmuch as our results were essentially the same with either dextrose or nonutilizable sucrose, it is probable that the myocardial and coronary

effects we observed were not metabolic but osmotic in character and were derived primarily from alterations in muscle tone. Similar osmotic effects of hypertonic solutions on muscle tone have been described by Barbour and Rapoport[1] in studies on the intact uterus of dogs.

SUMMARY AND CONCLUSIONS

An apparatus is described which will permit long perfusion of an isolated mammalian heart with several readily interchangeable perfusates at constant temperature and pressure.

Ringer-Locke perfusates containing excess concentrations of dextrose usually cause moderate and transient increase of the coronary flow, leading immediately to augmentation of the stroke amplitude.

The apparently similar myocardial and coronary stimulation observed with perfusates containing excess concentrations of nonutilizable sucrose suggests that all the sugar effects are osmotic rather than metabolic.

Perfusion with Ringer-Locke solution containing sucrose in place of dextrose results in early failure of the heart.

There is no evidence that long perfusion with an excess of dextrose results in the storing or building up of other reserve fuel.

The myocardial and coronary effects are essentially the same whether or not insulin is supplied with the excess of dextrose, whether or not the perfusates are adequately oxygenated, and whether or not the hearts have been previously damaged by drugs.

Although the activity of the frog heart which has been subjected to anoxic failure is promptly restored by the administration of dextrose, no such revival of a similarly depressed rabbit heart can be accomplished with dextrose alone.

There is no evidence from our experiments that dextrose furnished in greater than the usual physiologic concentration of 0.1 per cent offers more than a fleeting functional advantage to the isolated rabbit heart when perfused with Ringer-Locke solution.

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HEMODYNAMIC STUDIES IN EXPERIMENTAL CORONARY OCCLUSION*†

V. Changes in Arterial Blood Pressure

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THE published reports on the effect of experimental coronary artery occlusion on arterial blood pressure have concerned themselves almost entirely with the immediate changes which follow this procedure. There has been no unanimity expressed as to the sequence of events. Thus, in 1867, von Bezold[1] reported a fall in arterial blood pressure occurring simultaneously with the appearance of cardiac irregularities following coronary occlusion in rabbits. Cohnheim and Schulthess-Rechberg[2] made similar observations in dogs. Porter,[3, 4] who carried out extensive experimental researches in this field, observed that there was a short and rapid rise in arterial blood pressure immediately after the vascular occlusion in dogs and that in some experiments this was followed by a fall. Michaelis[5] reported a slow or rapid fall in arterial blood pressure after coronary ligation in rabbits. Wassiliewski[6] injected lycopodium spores into the coronary vessels of rabbits and dogs. Soon after the injection there was a rapid fall in blood pressure. In rabbits this was preceded by a rise.

Of the more recent experiments, Sutton and Lueth[7] observed a rapid fall in blood pressure amounting to 30 to 50 mm. Hg following partial compression of the dog's coronary artery. In vagotomized animals the vascular occlusion was followed by no alteration in the blood pressure. Feil, Katz, Moore, and Scott[8] observed "surprisingly small changes" in the arterial blood pressure following coronary artery occlusion in dogs. There was an apparently constant drop of only 5 to 20 mm. Hg in 6 out of 19 animals. In 4 dogs a temporary drop was followed by a return to normal or higher levels, and in 5 a rise of 10 to 30 mm. Hg took place. In every instance with premature beats and paroxysmal tachycardia a drop of 20 to 40 mm. Hg was recorded. Cox and Robertson[9] studied the blood pressure of dogs over a period of months before and after coronary occlusion and observed no appreciable differences between the preligation and postligation blood pressure levels.

The clinical observations dealing with blood pressure changes following coronary occlusion have been followed more thoroughly. It is

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‡Deceased.
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currently accepted that myocardial infarction is generally associated with a fall in arterial blood pressure. Fishberg, Hitzig, and King,[10] pointed out that this fall takes place only in those cases of myocardial infarction in which evidences of shock appear. They believe that in instances of myocardial infarction in which the clinical features are predominantly those of cardiac insufficiency with intense pulmonary engorgement, the blood pressure tends to be maintained at a level relatively close to that prevailing prior to the infarct, or it may even rise.

In a recently reported series of studies on experimental coronary occlusion in dogs, we have shown that the only hemodynamic changes which deviate appreciably from those observed in controls under similar experimental conditions were an immediate diminution in average cardiac output and delay in cyanide circulation time. These observations were based on a study of the changes produced by anesthesia alone, anesthesia followed by thoracotomy without coronary ligation, and by coronary ligation performed in the open chest,[11] in the closed chest (by the double carrick bend knot[12]), in denervated hearts,[13] and in stellate-ganglionectomized dogs.[14] Although an immediate fall in blood pressure was recorded following occlusion of the left anterior descending coronary branch under the various conditions mentioned above, with the exception of the denervated hearts this was no greater than that found in the control animals. From these observations it was concluded that this immediate fall in arterial blood pressure was due to the anesthesia or thoracotomy, and not to the vascular occlusion. In the sympatheticovagotomized dogs there was an immediate fall in blood pressure which exceeded that of the controls.

The present report concerns itself with further studies on the arterial blood pressure under the various experimental conditions mentioned above. The arterial blood pressure was measured by puncturing the femoral artery with a 19-gauge needle which was attached by a three-way stopcock to a syringe and mercury manometer. The readings were made during the immediate preligation period, during the immediate postligation period, twenty-four hours after the vascular ligation, and one week later. Eighty-two mongrel dogs weighing between 10 and 20 kilograms were employed in the experiments. The details of the experimental procedures are recorded in our earlier reports. Simultaneously with the blood pressure readings, other hemodynamic studies were carried out in a number of the dogs. All readings and tests were made under nembutal anesthesia.[11]

RESULTS

As will be seen in Table I, in which the preligation value is recorded as an average value for the group, or as 100 per cent, the anesthetic alone (Group A) produced no appreciable change other than a moder-

TABLE I

BLOOD PRESSURE CHANGES AFTER VARIOUS PROCEDURES

GROUP	*Average Mean Blood Pressure Changes in Mm. Hg*				*Average Per Cent Mean Blood Pressure Changes*			
	PRELIGATION*	POSTLIGATION†	24 HOURS LATER	ONE WEEK LATER	PRELIGATION	POSTLIGATION	24 HOURS LATER	ONE WEEK LATER
A Anesthesia controls	123 (10)‡	125 (10)	112 (6)	138 (4)	100	102	91	112
B Thoracotomy controls (No ligation)	148.3 (10)	133 (10)	117.7 (10)	132 (9)	100	90	80	89
C Thoracotomy + left anterior descending coronary branch ligation	152 (12)	127 (12)	94 (11)	99 (6)	100	84	62	65
D Left anterior descending coronary branch ligation (closed chest)	118 (10)	120 (10)	71 (5)	100 (3)	100	102	60	85
E Denervated heart: Left anterior descending coronary branch ligation (closed chest)	131 (10)	115 (10)	--	--	100	88	--	--
F Denervated heart: Left ventricular muscle ligation (closed chest)	128.5 (10)	125.1 (10)	--	--	100	97	--	--
G Thoracotomy + left anterior descending coronary branch ligation (stellate ganglia removed)	129 (10)	93 (10)	77 (10)	98 (4)	100	72	60	76
H Left ventricular muscle ligation (closed chest)	146 (10)	131 (10)	112 (10)	117 (7)	100	90	77	80

*Twenty minutes before ligation.
†Twenty minutes after ligation.
‡The figures in parentheses indicate the number of animals in each group.

ate drop (9 per cent) twenty-four hours after its administration. Within a week (possibly soon after twenty-four hours), the blood pressure returned to preligation levels. It will be observed, however, that following thoracotomy under anesthesia (Group B), the average arterial blood pressure dropped 20 per cent within twenty-four hours. The blood pressure returned to within 10 per cent of the preligation level within one week. These blood pressure changes must be considered as the control base line for the experiments to be described.

Ligation of the left anterior descending coronary branch, whether performed in the open chest (Group C) or by the closed chest method (Group D[12]), produced no appreciable immediate fall in blood pressure. However, twenty-four hours after the vascular occlusion the blood pressure was decidedly lower than in the controls. At the end of the week the arterial blood pressure still remained low in the open-chest experiments but had risen toward normal values in the closed-chest experiments.

The immediate postligation arterial blood pressure level was lower in the dogs with denervated hearts (Group E) than in the corresponding controls (Group F). It has already been suggested[13] that this may be due to the absence of the masking effect of the usually wide fluctuations in vasomotor tone in animals with nerves intact, and possibly also to the interruption of some of the nervous pathways for compensatory vasoconstriction. Twenty-four-hour and one-week readings were not made in these groups because of the high mortality. In the stellate-ganglionectomized dogs (Group G) coronary ligation was followed by an immediate sharp drop in blood pressure which reached 60 per cent of its preligation value at the end of twenty-four hours and showed a relatively slow return to normal by the end of one week. Other effects of stellate ganglionectomy on the sequelae of coronary occlusion have been recorded elsewhere.[14]

Of considerable interest were the changes in blood pressure following ligation of small portions of left ventricular muscle in the closed chest experiments (Group H). Study of the cardiac output in this group of animals revealed no appreciable change from the anesthesia controls. Nevertheless, the arterial blood pressure sank 23 per cent at the end of twenty-four hours as compared with 9 per cent in the control groups.

DISCUSSION

The observations herein recorded indicate that coronary artery ligation in the dog's heart produces a definite fall in blood pressure. This, however, becomes conspicuous only twenty-four hours after the vascular occlusion and generally persists for at least one week. Since most of the reported experiments were not concerned with successive studies on the blood pressure following coronary occlusion, this fact seems to have been overlooked. In spite of the immediate fall in

cardiac output, an immediate fall in blood pressure does not occur probably because of compensatory vasoconstriction.

In our previous reports we have shown that the cardiac output tends to rise after twenty-four hours and that, moreover, the blood volume is not materially affected by the coronary occlusion. In spite of this, however, the compensatory vasoconstriction decreases twenty-four hours after the vascular ligation. The temporary immediate vasoconstriction is probably attributable to the decrease in cardiac output which stimulates the vascular vasosensitive areas. After twenty-four hours these mechanisms become readjusted to the lower output. The exact nature of these adjustments remains obscure.

SUMMARY

1. Twenty-four hours after experimental occlusion of the left anterior descending coronary branch in dogs there occurs a decided fall in blood pressure which generally persists for at least one week.

2. Twenty-four hours after ligation of left ventricular myocardium by the closed chest method a fall in blood pressure also occurs. This fall is smaller than that following the vascular occlusion.

3. A comparison is made with control observations, and the mechanism for the decrease in blood pressure under these conditions is discussed.

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BUNDLE BRANCH AND INTRAVENTRICULAR BLOCK IN ACUTE CORONARY ARTERY OCCLUSION*†

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IN THIS report we have analyzed the disturbances in intraventricular conduction observed in 375 cases of acute coronary artery occlusion with reference to their incidence, clinical and electrocardiographic features, prognosis and pathogenesis. All records in which the QRS interval was prolonged to 0.12 sec. or more were considered. These included all types of bundle branch and intraventricular block. We have been impressed by the frequency of such intraventricular conduction disturbances in this disease and their association with a specific lesion in the heart, namely, infarction of the interventricular septum. The common occurrence of the latter has already been pointed out.[1]

Previous investigators[2-5] have demonstrated that bundle branch block is caused by involvement of the conduction system situated in the interventricular septum, usually as a result of disease of the coronary arteries. The association of bundle branch and intraventricular block with acute coronary occlusion has often been reported,[6-26] and a few authors[27-30] have drawn attention to its frequency. The fact that the sudden appearance of bundle branch block may be the first electrocardiographic sign of acute coronary occlusion has not been sufficiently stressed.

INCIDENCE

A review of the conduction disturbances in several large series of acute coronary artery occlusion reported in the literature[28, 30-38] revealed that bundle branch block was present in 6.7 per cent of 930 cases and intraventricular block in 7.3 per cent of 831 cases, a combined incidence of 12 per cent in 1058 cases. The highest figures, up to 28 per cent, were observed in the series of autopsy cases,[28, 36-38] indicating the increased mortality rate associated with intraventricular block. In our series of 375 patients defective intraventricular conduction, as evidenced by widening of the QRS interval to 0.12 sec. or more, was present in 57, or 15 per cent (Table I). Marked prolongation of the QRS interval to 0.18-0.20 sec. occurred in 4 patients, mod-

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TABLE I

BUNDLE-BRANCH AND INTRAVENTRICULAR BLOCK IN CORONARY OCCLUSION; CLINICAL AND POSTMORTEM DATA IN 57 PATIENTS

CASE	SEX	AGE	CLINICAL ATTACK	HYPERTENSION	CARDIAC ENLARGEMENT	HEART FAILURE	QRS DURATION	BLOCK	ONSET	DURATION	P-R	ECG	MORTALITY	POSTMORTEM: OCCLUSION	POSTMORTEM: INFARCTION
1. P.B.	M	47	1	?	++	++++	0.20	LBB	1 day	Permanent	0.30	?	0		
2. R.N.	F	66	2	+	+++	+++	0.18	LBB	1st record	Permanent	0.24	?	0		
3. M.E.	M	72	2	+	++	+++	0.18	RBB	20th day	Until death	0.18	T-1	+	LAD.	Ant. wall. L. V.; ant. sep.; sep. perfora.
4a. D.F.	M	58	2	+	+++	++++	0.16	LBB	1 day	Permanent	0.24	T-1	0		
4b. D.F.	M	59	3	+	+++	++++	0.18	RBB	1 day	Permanent	0.26	T-3	0		
5. D.B.	M	56	2	+	+	++	0.16	LBB	1 day	Until death	0.16	T-1	+	Acute and old LAD.	Anterior L. V.; lower half septum
6. M.C.	M	50	2	+	+++	++	0.16	I-V	1st record	2 weeks	0.20	?	0		
7. S.D.	F	47	1	+	+	0	0.16	LBB	1st record	Few weeks	0.22	?	0		
8. A.G.	M	48	2	+	+	+++	0.16	I-V	1st record	Until death	0.16	?	+	Old LAD and left circ.; acute right.	Post. L. V.; post. septum.
9. P.S.	F	55	2	+	+	++	0.16	I-V	1st record	Until death	0.14	T-1	+	Old LAD. and right; acute LAD.	Ant. & post. L. V.; entire septum.
10. R.W.	M	69	1	+	+	++	0.16	RBB	1 day	Until death	0.16	T-1	+		
11. L.B.	M	67	2	?	++	+++	0.15	LBB	Before attack	Permanent	A.F.	?	0		
12. J.B.	M	59	2	?	+++	+++	0.15	LBB	1st record	Until death	0.16	?	+	Old left circ. & acute right.	Apex L. V. & ant. sept.; aneurysm apex.
13. A.L.	F	57	2	+	++	+	0.15	LBB	1 day	Permanent	0.22	?	0		
14. S.F.	M	47	2	+	+	+++	0.15	RBB	1 day	Until death	0.16	T-1	+	Old rt. & acute LAD, left circ. & right.	Ant. & post. L. & Rt. V.; entire septum.
15a. S.G.	M	68	1	+	++	+	0.12	LBB	1st record	Permanent	0.16	T-1	0		
15b. S.G.	M	69	2	+	+++	+++	0.15	LBB	Gradual	Until death	0.16	?	+	Old LAD and right; acute	Old ant. L. V. and lower sep-

TABLE I—CONT'D

								Atypical							
16.	M.T.	M	66	2	+	++	+++	0.15	RBB	10 day	Until death	0.20	T-1	+	
17.	I.L.	F	78	2	+	++	+++	0.15	RBB	1st record	Until death	II.B.	T-3	+	Old LAD, left & right circ.; acute R. and LAD.	Post. L. & Rt. V.; post. septum.
18.	B.F.	M	41	2	+	++	+++	0.15	LBB	1st record	Permanent	0.18	T-1	0		
19.	E.L.	M	47	1	+	0	0	0.15	RBB	Before admission	Permanent	0.16	?	0		
20.	D.R.	M	62	2	?	++	+++	0.15	RBB	1st record	Until death	0.22	T-3?	+	Old & acute LAD; ant. & post. L.	Ant. & Post. L. V.; ant. 2/3 septum.
21.	J.S.	M	50	1	?	0	++++	0.15	I-V	1st record	Until death	0.15	T-1	+		
22a.	N.R.	M	57	2	+	+++	+++	0.12	LBB	1 day	Permanent	0.22	T1-2-3	0		
22b.	N.R.	M	57	3	+	+++	+++	0.15	LBB	39 day	Permanent	0.24	T1-2-3	0		
23.	D.F.	M	75	2	+	++	++++	0.14	LBB	1st record	Until death	0.40	T-1?	–	Acute & old right.	Post. L. V. with aneurysm
24.	M.G.	M	56	1	+	+++	+++	0.14	LBB	1st record	Permanent	0.20	?	0		
25.	M.G.	M	60	2	+	+	++	0.14	LBB	1st record	Until death	0.18	T-1	+		
26.	G.M.	M	35	1	+	0	+	0.14	LBB	1 day	1 day	0.16	T-1	0		
									RBB	2 day	Permanent					
27.	S.L.	M	67	3	?	+++	+++	0.14	RBB	1st record	Until death	0.16	T-3	+	Old LAD & right; acute right.	Post. L. V.; post. septum
28.	M.R.	M	60	1	+	++	+++	0.14	LBB	1st record	Permanent	0.10	?	0		
29.	E.D.	M	63	3	+	+++	++++	0.14	LBB	1st record	Permanent	0.16	?	+	Old LAD, L. & rt. circ.; acute LAD & RPD.	Post. L. V.; old ant. L. V.
30.	S.F.	M	86	1	0	0	0	0.14	RBB	1st record	?	0.14	T-3	0		
31.	E.M.	M	33	3	+	+++	+++	0.14	RBB	1st record	Permanent	0.24	?	+	LAD, L. & Rt. circ.	Ant. & post. L. V. and septum
32.	M.S.	M	73	1	+	++	+++	0.14	RBB	1st record	Permanent	0.14	?	0		
33.	I.G.	F	57	1	+	+	++	0.14	RBB	1 day	One day	0.20	T-3	0		
34.	M.K.	M	61	1	?	++	++	0.14	LBB	1st record	Permanent	0.20	T-1	0	LAD.	Ant. wall L. V.; ant. septum.

	CASE	SEX	AGE	CLINICAL ATTACK	HYPERTENSION	CARDIAC ENLARGEMENT	HEART FAILURE	QRS DURATION	BLOCK	ONSET	DURATION	P-R	ECG	MORTALITY	POSTMORTEM	
															OCCLUSION	INFARCTION
35.	O.L.	M	63	2	+	++	+++	0.14	I-V	1st record	Until death	0.16	T1-2-3	+	LAD; left and rt. circ.	Ant. & Post. L. V. and septum.
36.	M.L.	M	66	3	+	++	++++	0.13	I-V	3 day	Until death	0.16	T-1	+		
37.	W.B.	M	55	1	+	+	0	0.13	RBB	1st record	Permanent	0.14	?	0		
38.	A.W.	M	50	1	0	0	0	0.13	RBB	1st record	Permanent	0.16	T-1	0		
39.	J.S.	M	55	1	+	+	+	0.13	LBB	1st record	Permanent	0.14	T-1	0		
40.	L.D.	M	61	1	+	+++	+++	0.13	RBB	1 day	Permanent	0.14	T1-2-3	0	LAD and right	Ant. & post. L. V.; entire septum.
41.	C.A.	M	35	1	0	0	0	0.12	LBB	1 day	2 days	0.14	T-1	0		
42.	L.B.	M	65	2	+	+	+	0.12	LBB	1st record	Permanent	0.18	T-3	0		
43.	A.B.	M	65	2	+	++	++	0.12	LBB	1st record	Permanent	0.20	T1-2-3	0		
44.	C.B.	F	72	2	+	++	++	0.12	LBB	1st record	Until death	H.B.	T-3	+	Old left circ.; acute right	Post. L. & Rt. V.; Post. septum.
45.	D.C.	M	38	2	+	+	+++	0.12	LBB	1 day	Until death	0.22	T1-2-3	+		
46.	J.K.	M	55	3	+	+	++	0.12	I-V	3 week	Until death	0.22	T1-2-3	+	Old LAD & rt.; acute LAD; L. & Rt. circ.	Ant. & Post. L. V.; entire septum.
47.	A.L.	M	54	1	?	+	+	0.12	RBB	1st record	?	0.16	T-3	0		
48.	C.L.	M	49	1	+	+	+	0.12	LBB	1st record	Permanent	0.24	T-1	0		
49.	F.M.	M	62	2	0	+	++	0.12	I-V	1st record	Permanent	0.14	T-3	0		
50.	J.M.	M	73	3	+	++	++	0.12	LBB	1st record	Permanent	0.18	T1-2-3	0		
51.	E.R.	M	59	2	+	++	+++	0.12	LBB	1st record	Permanent	0.16	T-1	0		
52.	J.U.	F	57	4	+	+++	++	0.12	LBB	1st record	Permanent	0.18	?	0		
53.	A.Z.	F	53	2	+	+	++	0.12	LBB	Before attack	Until death	H.B.	T-3	+	Old LAD; L. & Rt. circ.; acute rt.	Post. L. & Rt. V.; post. septum.
54.	G.B.	M	59	2	+	+	++++	0.12	I-V	1 day	Until death	0.14	T1-2-3	+	Old L. & Rt. circ.; acute LAD.	Ant. L. V.; ant. septum.
55.	T.C.	M	31	1	0	0	0	0.12	I-V	1st record	Permanent	0.12	T-1	0		
56.	H.R.	M	50	2	+	+	+	0.12	LBB	1 day	Permanent	0.16	T1-2-3	0		
57.	S.M.	M	65	2	+	0	+	0.12	LBB	1 day	1 day	0.18	T-1	0		

erate prolongation to 0.14-0.16 sec. in 31 patients, and slight prolongation to 0.12-0.13 sec. in 22 patients.

Sex and Age.—This group of 57 patients included 48 males and 9 females, a ratio of 5.4:1, whereas the ratio for patients with normal conduction was 3.7:1. The average age of 59 years for the group was slightly higher than that of 55 years for the patients without conduction defects (Table II).

CLINICAL FEATURES

Incidence of Hypertension and Heart Failure.—Defective intraventricular conduction was usually associated with long-standing hypertension, cardiac enlargement, and congestive heart failure, the respective incidence of each being 77, 84, and 92 per cent, which was definitely higher than in our large control series (Table II). When the QRS interval measured more than 0.15 sec., cardiac enlargement and failure were practically universal.

TABLE II

BUNDLE BRANCH AND INTRAVENTRICULAR BLOCK IN ACUTE CORONARY ARTERY OCCLUSION (375 CASES)

	QRS 0.12-0.13 SEC.	QRS 0.14-0.20 SEC.	TOTAL CASES	NORMAL CONDUCTION (CONTROL GROUP)
No. of cases	22	35	57 (15%)	318
Average age	58.5	59	59	55
Sex: Male	19	29	48 (5.4:1)	3.7:1
Female	3	6	9	
Attacks: 1st	8 (26%)	13 (24%)	21 (35%)	56%
2nd to 4th	14 (64%)	25 (66%)	39 (65%)	44%
Hypertension	17 (77%)	27 (77%)	44 (77%)	62%
Cardiac enlargement	17 (77%)	31 (89%)	48 (84%)	55%
Heart failure	18 (82%)	33 (94%)	51 (92%)	68%
Mortality	6 (27%)	18 (51%)	24 (42%)	23%

Incidence of Previous Attacks.—Defective intraventricular conduction was more common in patients who had sustained previous attacks of coronary occlusion than in patients in their initial attack. Two-thirds of the patients in this group were suffering from a second or later attack, whereas less than half the patients with normal conduction had had a previous occlusion.

The importance of repeated attacks of occlusion in the development of bundle branch block is illustrated by a patient (Case 4) observed during three attacks of coronary occlusion over a period of six years (Fig. 1). Following his first attack the QRS interval measured 0.10 sec., and after the second attack it became prolonged to 0.14 sec. After the third attack it increased to 0.18 sec., and the electrocardiographic pattern changed from left to right bundle branch block. A similar instance was that of a 69-year-old man (Case 15) who was observed clinically during two attacks of coronary occlusion. After the first attack the

QRS became prolonged to 0.12 sec., and the electrocardiogram gradually assumed the appearance of partial bundle branch block. One year later he suffered another occlusion and typical left bundle branch block developed, the QRS measuring 0.15 sec. Necropsy revealed that the first occlusion had involved the left coronary artery, and the second, the right.

Time of Onset.—The conduction defect usually developed soon after the coronary artery occlusion, although the exact time of onset could not be determined accurately in many cases, for few electrocardiograms taken prior to admission to the hospital or prior to the attack were available. In sixteen patients admitted on the first day of the attack

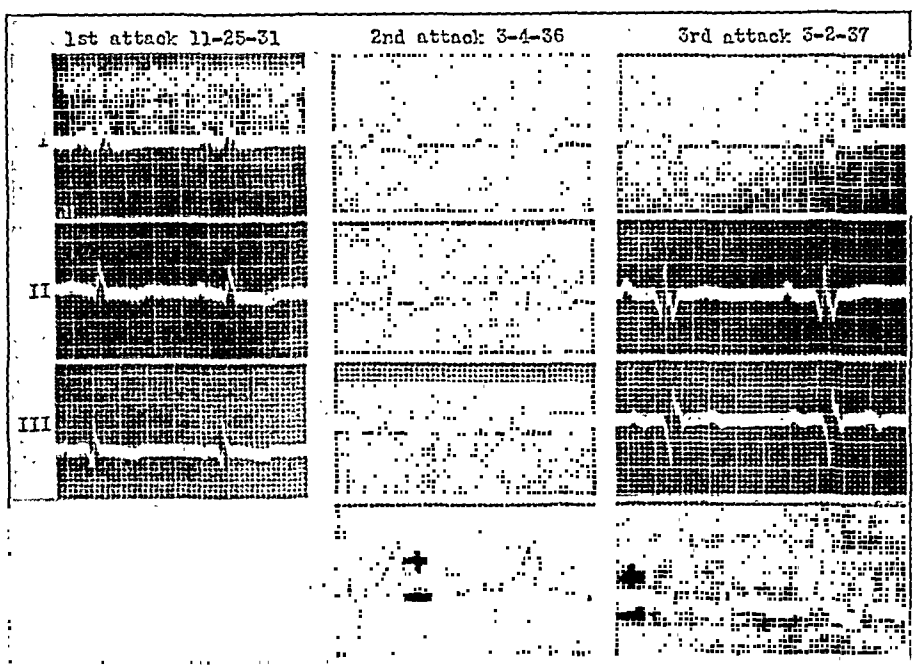

Fig. 1.—Case 4. Male, age 59 years. Effect of repeated attacks of coronary occlusion on intraventricular conduction. The QRS interval increased from 0.10 sec. in the first attack to 0.14 sec. during the second and 0.18 sec. during the third. Simultaneously the P-R interval increased from 0.20 sec. to 0.26 sec. The sudden increase in A-V and intraventricular block in each attack was of great diagnostic significance. The patient recovered.

the intraventricular block was already present. In thirty-two patients who entered at intervals of two to twenty days following the attack the conduction defect was observed in the first electrocardiogram obtained. Five patients (Cases 36, 16, 3, 46, 22) developed intraventricular block while under observation on the 3rd, 10th, 20th, 21st and 39th days, respectively (Figs. 2 and 11). In the four remaining patients (Cases 4, 11, 15, 53), some degree of intraventricular block was present in records taken prior to the last attack in which we treated them. Even in these cases, however, the intraventricular block was related to coronary occlusion; in three it had set in following a previous attack and had increased in degree following the later one (Fig. 1).

Duration.—In marked contrast to auriculoventricular block[39] and other arrhythmias[40] in coronary artery occlusion, intraventricular block was usually permanent. The conduction defect persisted in 23 patients until death, which occurred at intervals of one day to several months following the onset of their attack. In 27 patients who survived, the conduction defect was still present in records taken several months to two years later (Figs. 1, 6, 9). In six patients, however, the intraventricular block was transient and disappeared or diminished in degree within several days or weeks. The transition to normal conduction was sudden in four of these patients (Figs. 3, 4, Cases 6, 33, 41, 57). In one patient with typical left bundle branch block (Case 7) there was gradual lifting of the block; after one week every other beat was con-

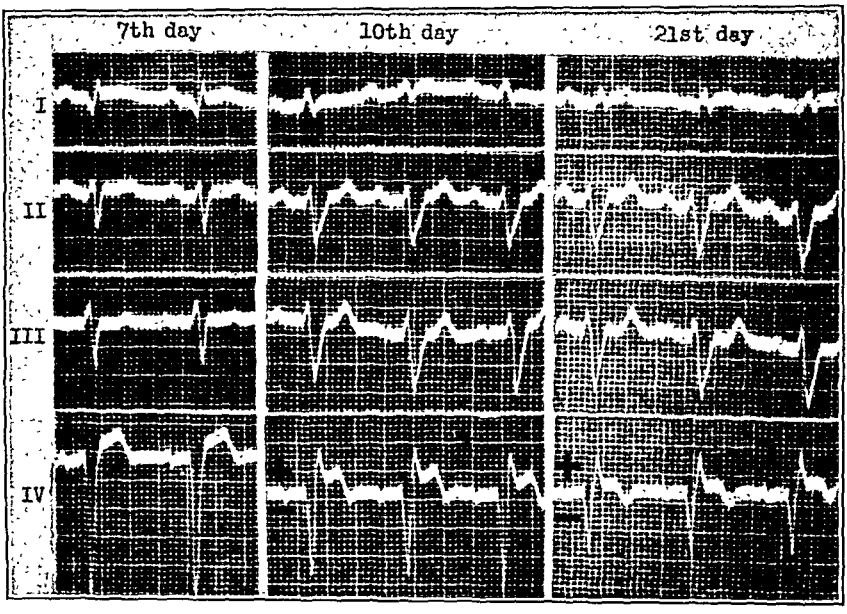

Fig. 2.—Case 11. Male, age 66 years. Sudden appearance of atypical bundle branch block (right?) 10 days after an acute coronary occlusion. The QRS interval is prolonged to 0.15 sec. The typical Q_1 T_1 pattern of anterior wall infarction, present at the onset of the attack, is masked by the conduction defect, except in the precordial lead. The patient died of heart failure during the fourth week.

ducted normally, the conduction defect being present in alternate beats only; it then became more intermittent, appearing only in isolated beats, and finally, after several weeks, there was complete disappearance of the left bundle branch block (Fig. 5).

Symptoms and Physical Signs.—The appearance of bundle branch or intraventricular block did not give rise to specific symptoms. Although severe heart failure was present as a rule, it was attributable to the coronary occlusion and not to the block. It must be kept in mind, however, that complete A-V heart block rarely may result from bilateral bundle branch block[5, 11, 15, 27, 41] and produce an Adams-Stokes syndrome. Thus in Case 26 the sudden onset of syncope and slowing of the pulse to less than 40 was associated with the appearance first of left and then of right

bundle branch block, suggesting that the syncope was due to complete A-V block resulting from involvement of both bundle branches simultaneously.

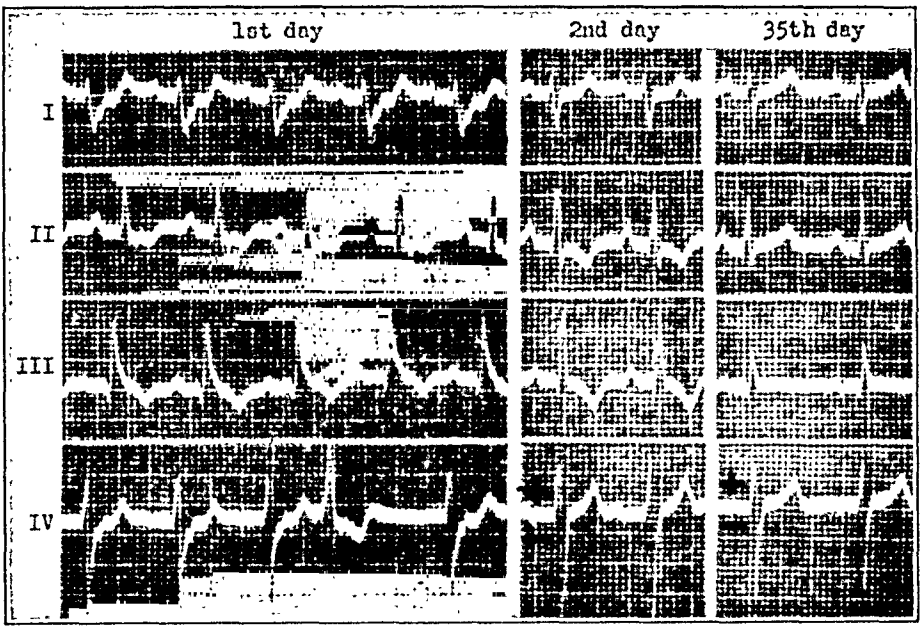

Fig. 3.—Case 33. Female, age 57 years. Transient right bundle branch block on the first day of acute coronary occlusion; the QRS interval is prolonged to 0.14 sec. On the 2nd day there is normal conduction with a T_2 T_3 pattern typical of posterior wall infarction. The electrocardiogram returns to normal on 35th day. The patient recovered.

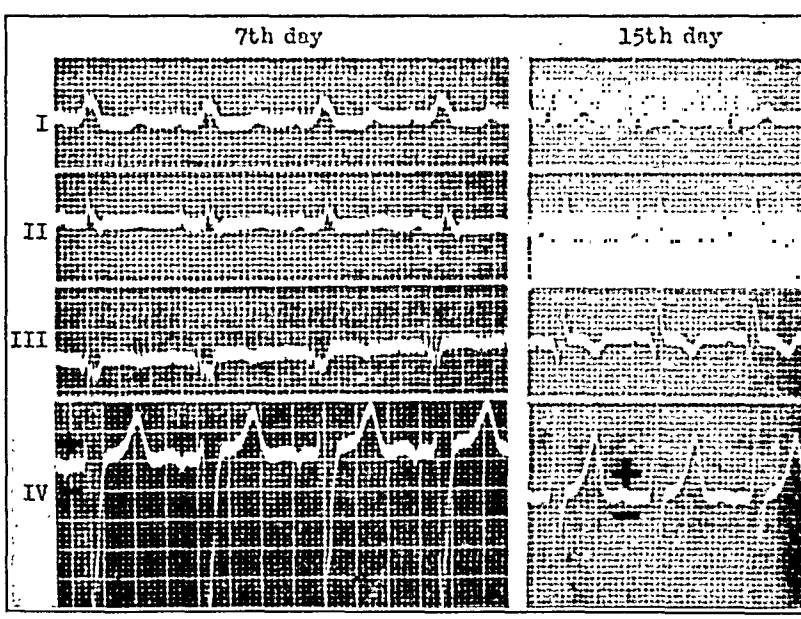

Fig. 4.—Case 6. Male, age 50 years. Transient intraventricu'ar block following coronary artery occlusion, lasting two weeks. The intraventricular block masks the characteristic signs of infarction. With return of normal conduction, the typical Q_3 T_3 pattern of posterior wall infarction appears. The small initial positive deflection in the precordial lead in the first record can be ascribed to the intraventricular block. The patient recovered.

On examination our patients did not present the signs of bundle branch block described by King and McEachern,[42] palpable reduplication of the apical impulse being observed only occasionally and splitting of the first heart sound in only four cases. Although diastolic gallop rhythm was present in 60 per cent of the cases, a higher incidence than existed in a larger series of unselected cases of coronary occlusion previously reported,[43] it was probably associated with the greater frequency and degree of heart failure in the presence of bundle branch block.

ELECTROCARDIOGRAPHIC FEATURES

Types of Block.—Left bundle-branch block of the common type, as evidenced by left axis deviation and widening of the QRS interval to

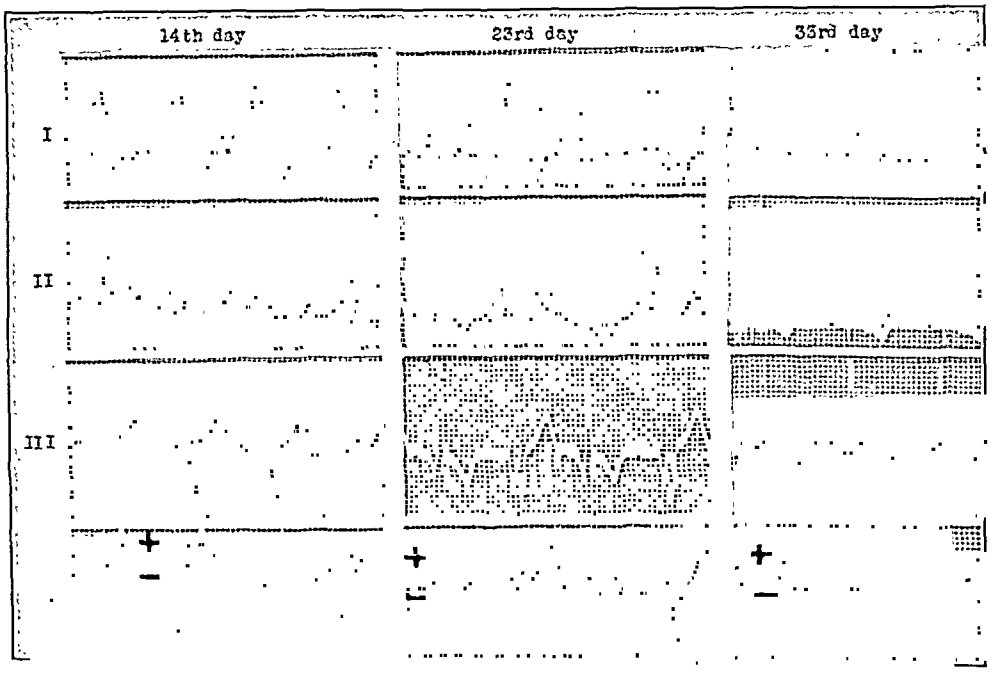

Fig. 5.—Case 7. Female, age 47 years. Transient and intermittent left bundle-branch block following acute coronary occlusion. The bundle branch block is constant until the 4th week, then every alternate beat is conducted normally, resulting in 2:1 bundle branch block. The latter disappears on the 33rd day. The bundle branch block masks the Q_3 T_3 pattern of posterior infarction, present in the normally conducted beats. The initial positive deflection is absent only when bundle branch block is present. The patient recovered.

0.12 sec. or more, occurred 29 times (Fig. 5). Typical right bundle branch block, indicated by right axis deviation and widening of the QRS complex, was observed in seven cases (Fig. 3). In addition there were nine instances of atypical right bundle branch as classified by Wilson and his associates,[44-46] characterized by a large, broad S-wave in Lead I, regardless of axis deviation (Fig. 1). In this type the QRS deflection in Lead I may be very small (Fig. 2). Finally, ten records fulfilled none of the above criteria and were classified as intraventricular block; in some of these the QRS complex was of low voltage (Fig. 4). It is thus seen that right bundle branch block was much more frequent in these

cases of coronary occlusion than had been reported previously in bundle branch block from all causes,[3, 4, 47] but this is due in great part to the new criteria of Wilson. Several records heretofore considered intraventricular block were classified as right bundle branch block.

The Distortion and Variability of Bundle Branch Block.—The bundle branch block pattern following infarction was often distorted by the presence of low voltage, prominent S-T deviations, and variations in the direction of the T-waves. This had already been observed clinically[29] and also experimentally[48] by simultaneous ligation of a coronary artery and cutting of a bundle branch. The myocardial infarction, as well as the location of the bundle branch lesion, is important in determining the electrocardiographic configuration.

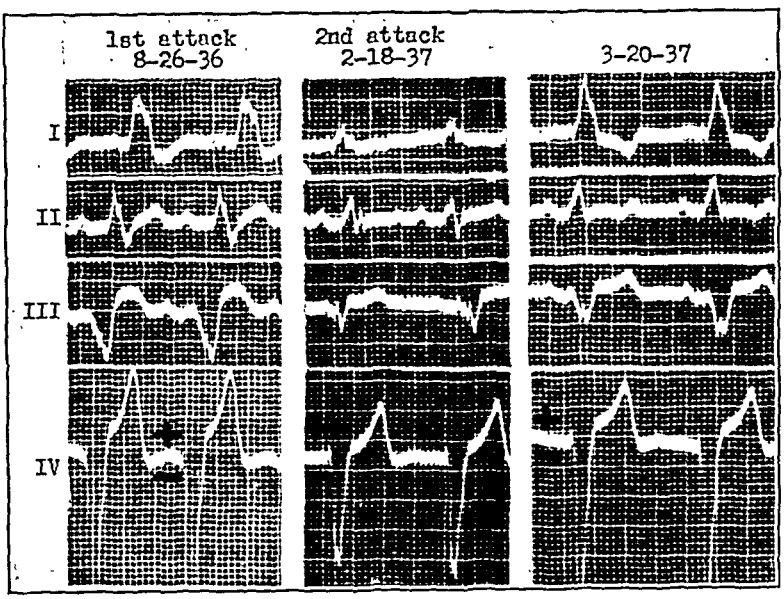

Fig. 6.—Case 2. Female, age 66 years. Variation in configuration of the ventricular complexes in bundle branch block. Following the 1st attack of coronary occlusion typical left bundle branch block developed. After the 2nd attack the ventricular complexes became very low and bizarre, the typical configuration of bundle branch block returning several weeks later. The characteristic signs of infarction are masked by the conduction defect. The patient recovered.

Furthermore, while bundle branch block ordinarily is fixed in appearance, following coronary occlusion it may vary from record to record, as illustrated by Case 2 (Fig. 6) in which typical left bundle branch block was present on admission soon after the attack. Subsequently the ventricular complexes assumed a bizarre form with very low voltage, and finally left bundle branch block returned. Another interesting example was Case 14 in which intraventricular block was present on the day of the attack (Fig. 7). On the third day typical right bundle branch block appeared but was again replaced on the next day by intraventricular block without axis deviation; the patient died on the fifth day, and necropsy revealed massive infarction of the entire interventricular septum.

Not only may the electrocardiographic pattern vary from day to day, but the bundle branch block may shift suddenly from left to right and vice versa. Thus in Case 4 left bundle branch block appeared after the second attack of coronary occlusion and was replaced by atypical right bundle branch block immediately after a third attack (Fig. 1). In Case 26 left bundle branch block on the second day of the attack was followed by right bundle branch block on the third day (Fig. 8).

These variations in the appearance and direction of the ventricular complexes depend upon two factors: first, the extent of the infarction and of the surrounding inflammatory reaction may change rapidly, and, second, the degree of ischemia of the conduction system may vary as a result of variations in the coronary blood flow. A diminution in the latter may produce a transient functional impairment in conduction

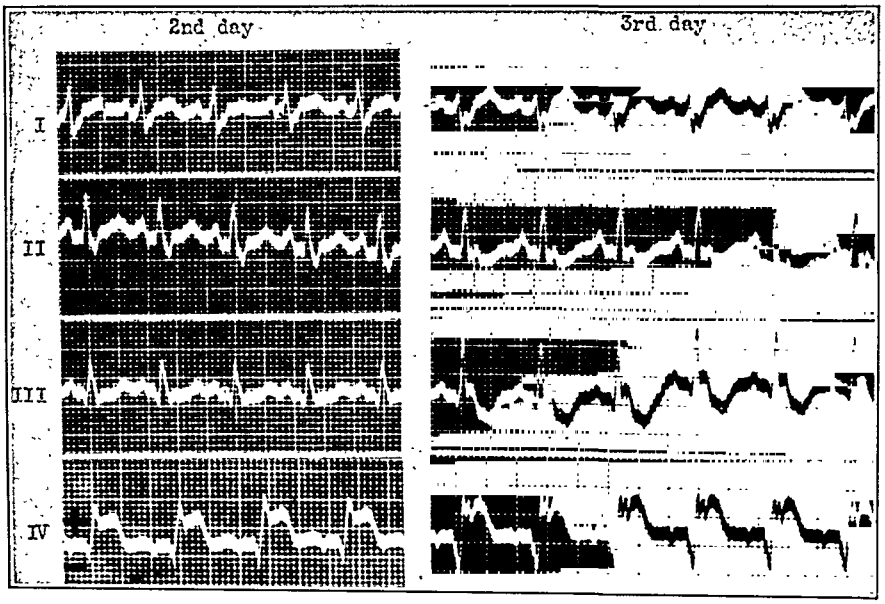

Fig. 7.—Case 14. Male, age 47 years. Intraventricular block on 2nd day (QRS 0.12 sec.) progressing to typical right bundle branch block on 3rd day (QRS 0.15 sec.). The precordial lead is characteristic of anterior wall infarction. Death occurred from cerebral embolism on 5th day. Autopsy showed infarction of the anterior and posterior surfaces of the heart and massive infarction of the entire interventricular septum, due to acute occlusions of both the left and right coronary arteries.

outside the infarcted area, resulting in the bizarre electrocardiographic pattern of interventricular block. Of considerable importance in this respect is the effect of tachycardia, which increases the degree of ischemia already present, and leads to functional fatigue of the conduction system. Electrocardiographically this often resulted in very marked alterations in the ventricular complexes which disappeared when the tachycardia ceased (Figs. 8 and 9).

Electrocardiographic Signs of Infarction in the Presence of Bundle Branch Block.—Serial changes in the S-T interval and T-wave permitted a diagnosis of acute infarction in two-thirds of the cases. Nineteen cases presented the T_1 pattern associated with anterior wall infarction and

nine the T_3 pattern of posterior infarction; in ten there were changes in all three standard leads suggesting both anterior and posterior infarction. This electrocardiographic localization was confirmed at autopsy in most

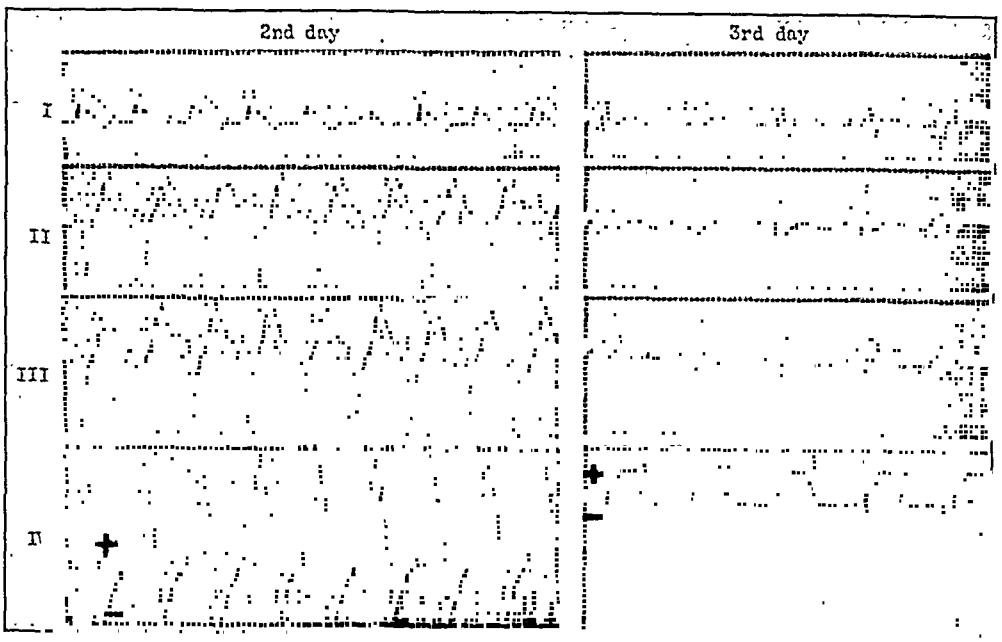

Fig. 8.—Case 26. Male, age 35 years. Transient atypical left bundle branch block associated with auricular paroxysmal tachycardia, followed by permanent right bundle branch block. The record, particularly the precordial lead, is characteristic of acute anterior wall infarction. The patient recovered.

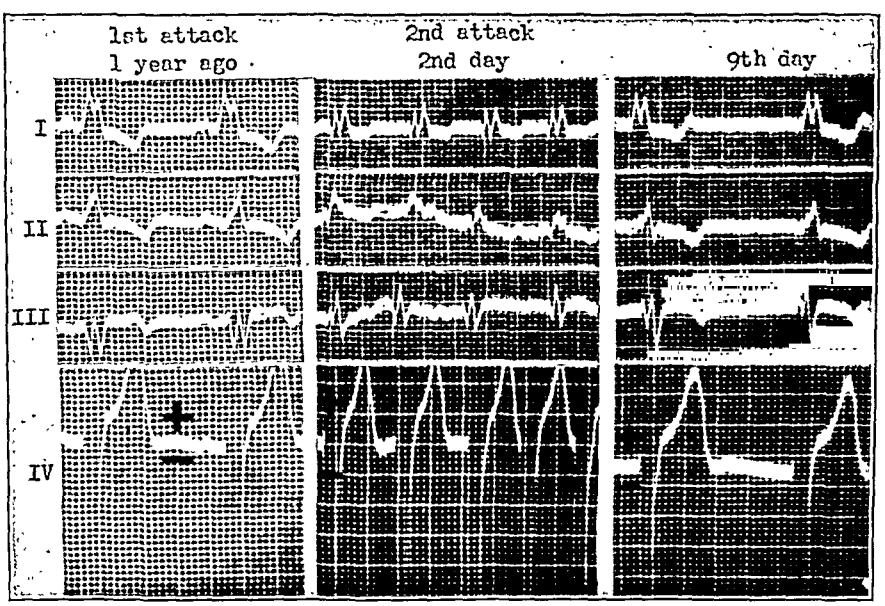

Fig. 9.—Case 11. Male, age 67 years. Effect of tachycardia on bundle branch block. Permanent left bundle branch block developed following 1st attack of coronary one year before. Sudden onset of auricular fibrillation with rapid ventricular rate following 2nd attack. The ventricular complexes become distorted and resemble those seen in intraventricular block. Following slowing of the ventricular rate by digitalis, the complexes reassume the characteristic configuration of left bundle branch block. The patient recovered.

cases, although in a few instances the electrocardiogram was of the T_1 or T_3 type alone, and autopsy examination showed infarction of both surfaces.

In nineteen, or one-third, of the patients, the bundle branch block masked the electrocardiographic signs of myocardial infarction, that is, characteristic progressive changes in the S-T interval and T-wave failed to appear. This observation has also been made by other authors.[18, 29, 49-51] The more marked the intraventricular conduction defect, the less often did the typical changes of infarction appear. Thus in all but one of these cases the QRS interval measured at least 0.14 sec. Since the classical clinical signs of coronary occlusion were usually present, the diagnosis was rarely in doubt despite the absence of characteristic electrocardiographic changes. Even in cases of this type serial electrocardiograms may be useful, for the bundle branch block may remit and changes characteristic of infarction may then appear (Figs. 4 and 5).

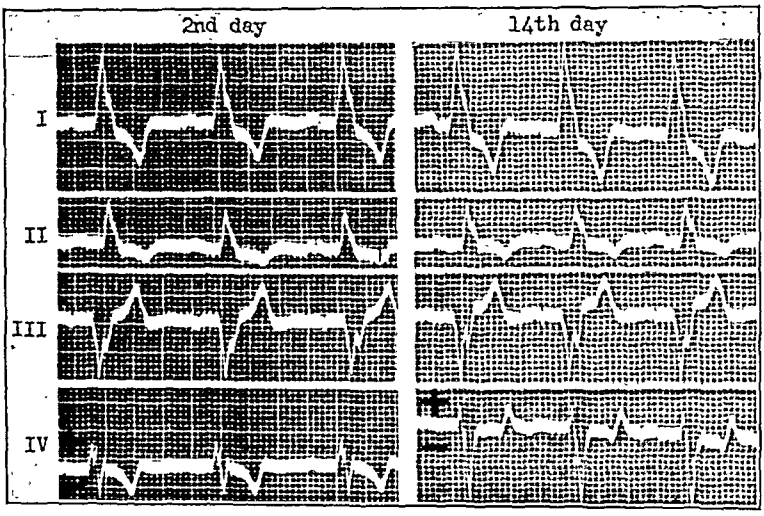

Fig. 10.—Case 13. Female, age 57 years. Typical left bundle branch block following 2nd attack of coronary occlusion. The conduction defect masks the signs of infarction in the standard leads, but progressive changes in the T-wave are observed in the precordial lead. The patient recovered.

The Precordial Lead in the Presence of Bundle Branch Block.—Unlike the standard leads, the precordial lead may be of diagnostic aid in the presence of bundle branch block, for characteristic progressive S-T and T-wave changes may appear in this lead alone (Figs. 10 and 11).

We have elsewhere[54] discussed the importance of an absent or very small initial positive deflection in the precordial lead in the diagnosis of coronary occlusion with anterior wall infarction. However, other authors[17, 55, 56] as well as we have pointed out that this deflection is occasionally absent and frequently very small in bundle branch block not associated with myocardial infarction, a fact illustrated by Cases 6 and 7. In both of these cases with posterior wall infarction this deflection returned to normal when the bundle branch block disappeared (Figs. 4

and 5). Nevertheless, certain observations suggest that in many cases of bundle branch block the absent or small initial deflection is produced by anterior wall infarction. In 23 out of 27 cases with bundle branch block, the absent or very small initial deflection could be explained in this way, for the electrocardiogram was of the T_1 or $T_{1, 2, 3}$ pattern of anterior or both anterior and posterior infarction. Furthermore, post-mortem examination in 12 cases revealed infarction of the anterior wall in 11 cases, and infarction limited to the posterior wall in one, whereas in the entire series the incidence of anterior and posterior infarction was the same. Hence in most cases the abnormal initial positive deflection may be considered a presumptive sign of infarction of the anterior wall even

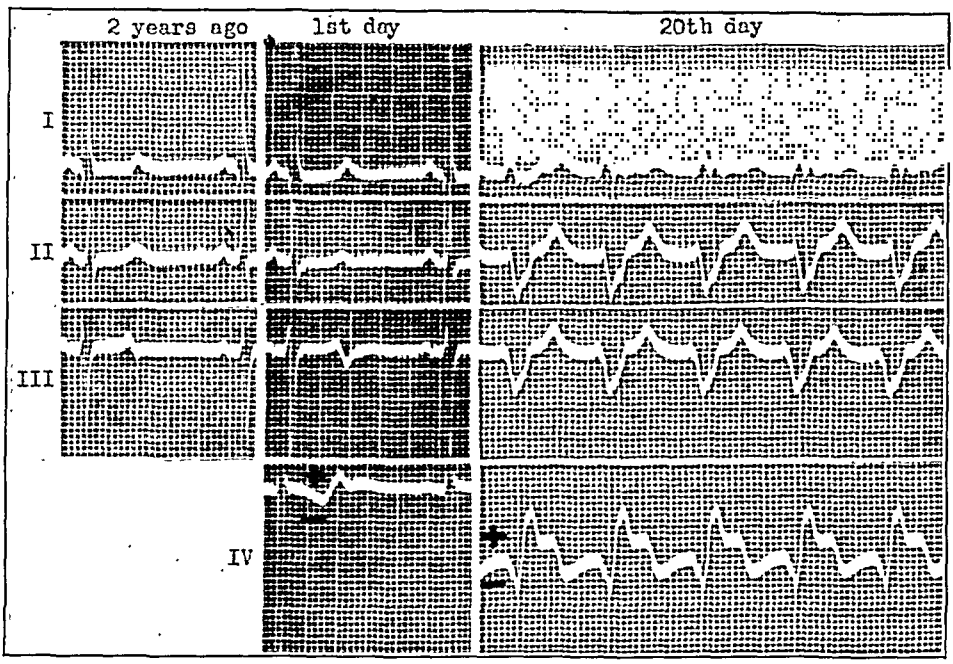

Fig. 11.—Case 3. Male, age 72 years. Sudden onset of atypical bundle branch block (right?) on the 20th day of attack, associated with idioventricular rhythm, rate 95. The precordial lead is characteristic of anterior wall infarction. There was a concomitant recurrence of precordial pain and shock, increase in heart failure, and appearance of a harsh systolic murmur and thrill suggestive of septal perforation, verified at autopsy. There was massive infarction of the septum with perforation, and infarction of the anterior wall of the left ventricle, due to occlusion of the left anterior descending artery.

when bundle branch block is present, although occasionally the latter alone is the cause.

Association of Bundle Branch Block With A-V Block and Other Arrhythmias.—Disturbances in intraventricular conduction were frequently associated with defective A-V conduction. Thus the P-R interval was prolonged to 0.20 sec. or more in 20 patients, an incidence twice as high as in patients with normal conduction[39]; in 7 patients it ranged from 0.24 to 0.40 sec. (Fig. 1). Complete heart block occurred in 3 cases (17, 14, 53). The association of bundle branch block with impaired A-V conduction received early emphasis in the literature.[2, 52] In several large series[3, 4, 36] of unselected cases of bundle branch and intraventricu-

lar block, the incidence of heart block ranged from 9 to 23 per cent. It is also noteworthy that in 13 of 15 cases of heart block following acute coronary occlusion described by Schwartz[50] there was, in addition, intraventricular block. These observations and our own suggest that the underlying cause for both A-V and intraventricular block in coronary artery occlusion is the same, i.e., occlusion of the specific arteries to the septum with infarction of the region of the A-V bundle and its branches. The septal infarct which we believe to be the cause of the bundle branch block may either extend high enough to involve the A-V node or bundle, or, as suggested previously,[5, 27] the infarct may involve both bundle branches simultaneously and thus produce defective A-V conduction.

Other arrhythmias were associated with bundle branch block no more often than with coronary artery occlusion in general.[40] The arrhythmias encountered, in addition to premature beats, were auricular fibrillation, 3 (Fig. 9); paroxysmal auricular or nodal tachycardia, 4 (Fig. 8); and ventricular tachycardia, 2 (Fig. 11). Special emphasis has been placed by many authors on the latter as a complication of coronary artery occlusion,[40] and it is interesting that several[27, 34, 53] have ascribed this arrhythmia to an infarct in the septum, the same lesion underlying bundle branch block. Yet in the 375 cases studied, only four instances of ventricular tachycardia were encountered, despite the frequency of septal infarction, and only two were associated with bundle branch or intraventricular block. In one of these cases examined post mortem (Case 3), the ventricular tachycardia and bundle branch block were found to be associated with massive septal infarction and septal perforation, suggesting that the view of the above authors may hold true in some cases.

DIAGNOSTIC SIGNIFICANCE

Diagnostic Significance of Bundle Branch Block in Acute Coronary Occlusion.—The sudden appearance of defective intraventricular conduction, transient or permanent, should suggest the possibility of recent coronary artery occlusion, even when typical clinical or electrocardiographic signs are lacking, particularly when associated with the onset of shock or heart failure. For example, one patient (Case 4) was observed in three attacks of pulmonary edema during six years, each attack associated with sudden prolongation of the QRS interval, and the third with a shift from left to right bundle branch block (Fig. 1). Because of these changes coronary occlusion was suspected each time and confirmed later by clinical observation. Similarly, in Case 7 the symptoms at first suggested acute cholecystitis, but coronary occlusion was suspected when bundle branch block was observed in the electrocardiogram (Fig. 5). This was corroborated when typical electrocardiographic changes became evident following the disappearance of the conduction defect. Furthermore, another occlusion or extension of the infarction should be suspected when bundle branch or intraventricular block suddenly develops several

days or weeks after an occlusion. Of five such cases, the onset of the bundle branch block was associated with a recurrence of precordial pain and shock in four, and post-mortem confirmation of another occlusion was obtained in the two cases in which an autopsy was performed (Cases 3 and 46).

Relation of Coronary Occlusion to Permanent Bundle Branch Block.—Since bundle branch or intraventricular block may become permanent following coronary occlusion, it may be the only electrocardiographic evidence that the patient has suffered a coronary occlusion in the past.[34] Thus 10.8 per cent of 576 cases of bundle branch and intraventricular block from all causes[3, 36] were associated with a known previous coronary artery occlusion. In a smaller series of bundle branch block cases studied by us,[57] 16.5 per cent followed acute coronary artery occlusion.

PROGNOSTIC FEATURES

The presence of bundle branch or marked intraventricular block adds to the seriousness of acute coronary artery occlusion, being associated with a mortality rate of 42 per cent as compared to 23 per cent in patients with normal conduction (Table II). The course of the illness in such patients is severe because of the greater degree of congestive failure and cardiac enlargement. Not only is the coronary artery sclerosis usually advanced, but at necropsy evidence of previous closure of one or more coronary arteries is almost universal. As a rule the increase in mortality and the severe heart failure occurred in the cases in which the QRS interval measured 0.14 sec. or more. Only occasionally was bundle branch block present without evidence of cardiac failure or enlargement (Table I). The mortality rate and incidence of heart failure were not influenced by the type of conduction defect, being the same whether left or right bundle branch block or intraventricular block was present.[3]

POST-MORTEM OBSERVATIONS

Site of Occlusion.—Necropsy, performed in 20 cases, revealed that the incidence of defective intraventricular conduction was the same whether the right or the left coronary artery was occluded. A recent occlusion was present in the left coronary artery in 7 cases, in the right in 5 cases, and in both arteries in the remaining 8. In addition, one or more arteries had been previously occluded in 16 of the 20 hearts, explaining the extensive myocardial damage usually observed.

Site of Infarction.—As one would expect from the foregoing figures, acute infarction of the anterior and posterior walls occurred with equal frequency. The anterior surface was involved in 6 cases, the posterior surface in 6 cases, and both surfaces simultaneously in the remaining 8.

The most consistent finding at necropsy was infarction of the interventricular septum, which was present in four-fifths of the cases. When the QRS interval measured more than 0.14 sec. infarction of the septum

was practically universal, whereas in patients with normal intraventricular conduction it occurred in only half the cases.[1] Furthermore, the incidence of defective conduction in 30 hearts with septal infarction was 43 per cent, while in 19 hearts in which the infarction spared the septum it was only 21 per cent. It appears, therefore, that the presence of septal infarction following acute coronary artery occlusion doubles the frequency of bundle branch or intraventricular block.

Cardiac Enlargement.—Intraventricular or bundle branch block was usually associated with considerable cardiac enlargement. The cardiac weight ranged from 400 to 490 gm. in seven cases, from 500 to 590 gm. in ten cases, and was 730 gm. in the remaining case, the average being 505 gm. In comparison, the average cardiac weight was only 440 gm. in 30 patients with normal intraventricular conduction who died of coronary occlusion; one-third of these hearts weighed less than 400 gm. The relation of cardiac enlargement to the pathogenesis of bundle branch block will be discussed below.

PATHOGENESIS OF BUNDLE BRANCH BLOCK

Anatomical Basis.—Since the main bundle branches run within the interventricular septum, one would expect bundle branch block to result from injury to this region. In animals septal infarction produced by ligation of the septal artery results in bundle branch block,[41, 51, 58-61] with few exceptions.[34, 62] In our series septal infarction was found in four-fifths of the cases. When the QRS interval was 0.14 sec. or more, septal infarction was constant. The obstruction to conduction is probably situated high up in the septum in the main bundle branches or their larger subdivisions. This would explain the frequency of associated disturbances in A-V conduction since these would be likely to occur when the infarct extended high enough to involve the A-V node or bundle. In mild degrees of intraventricular block the lesion may be lower down near the apex[2, 47] or in the subendocardial Purkinje system, despite the objection[29, 62-67] that the latter is resistant to ischemia. This would account for the absence of gross septal infarction in one-fifth of the cases with some degree of intraventricular block. However, it is not unlikely that minute study of the septum and bundle branches would have revealed some damage, or the block may have been the result of other factors such as anoxemia, as will be discussed later.

Normal Intraventricular Conduction with Septal Infarction.—Although high-grade intraventricular and bundle branch block were associated as a rule with septal infarction, the latter may be extensive and yet conduction may remain normal. Thus in only two-fifths of 30 cases with gross septal infarction studied previously[1] was there impaired intraventricular conduction, and other authors have described similar cases.[63, 68] Gross[64] offered two possible explanations. First, the specific blood supply to the conduction system may not be involved, despite closure of the main coronary vessels, for the occlusion may occur distal

to the origin of the septal branches.[36] Second, the anastomosis between the left and right coronary arteries in the septum may be so profuse that, when occlusion of one artery occurs, anastomotic channels from the patent vessel maintain an adequate circulation to the conduction system. Most of the anatomical and experimental evidence[62, 69-73] supports this view, although Mahaim[27] believes that there are few anastomotic vessels in the septum.

Correlation of Site of Occlusion and Type of Bundle Branch Block.—Since the right bundle branch is supplied almost exclusively by the septal branch of the left anterior descending artery, right bundle branch block should result from occlusion of this artery.[63, 64, 68, 73] Similarly, both the left and right coronary arteries theoretically should be occluded to produce left bundle branch block, for the left bundle is supplied by both vessels. Intraventricular block should be more common with left coronary occlusion, since this vessel provides the greater part of the blood supply to the ramifications of both bundle branches. Several authors[27, 30, 74] have utilized these anatomical observations in the attempt to localize the site of occlusion or infarction from the type of conduction defect. We agree with others[28, 50] that this cannot be done accurately, for our autopsy material fails to show agreement between the theoretical expectations and the actual vessels occluded. Occlusion of the right coronary artery was as frequent as that of the left, irrespective of the existing type of bundle branch block. Furthermore, multiple acute and old occlusions were usually present, so that it was very difficult to determine which occlusion was the cause of the conduction defect. Similarly, no correlation could be made between the type of conduction defect and anterior or posterior wall infarction. It is evident, however, that in our experience right coronary artery occlusion led to bundle branch block of either type more often than was to be expected from the distribution of the blood supply to the conduction system.

Transient Bundle Branch Block.—Anoxemia: Although infarction of the interventricular septum is the usual basis for bundle branch or intraventricular block in coronary artery occlusion, we have seen that in a few cases the conduction defect was transient and that occasionally septal infarction was not found at necropsy. In these the block may have been functional in nature, induced by anoxemia of the conduction system. The influence of anoxemia on conduction through the bundle branches and their ramifications is still a matter of dispute, the conduction system being found resistant by some investigators[65-67] and sensitive by others.[7, 75-79] It is noteworthy that transient bundle branch block has been observed during an attack of angina pectoris,[80, 81] suggesting that myocardial ischemia may result in functional fatigue of the conduction system.

In coronary occlusion several factors may lead to fatigue of the conduction system in the absence of septal infarction. As a result of shock

and drop in blood pressure, the cardiac output, and therefore the coronary circulation, are reduced. Robinson and Auer[82] attributed to coronary insufficiency the bundle branch block occurring in animals after the induction of anaphylactic shock. The effect of diminished cardiac output on coronary flow is enhanced by the heart failure which is very common in cases with bundle branch block. Transient bundle branch block has not infrequently been observed in congestive heart failure without occlusion.[7, 22, 76-78, 83-85] Two of our six cases of transient bundle branch block occurred in patients with severe failure; one was associated with severe shock. Finally, tachycardia may further burden a coronary circulation already impaired by occlusion and so induce bundle branch block which disappears with the cessation of the rapid rate.[76, 77, 86, 87] In Case 26 transient left bundle branch block appeared during a paroxysm of auricular tachycardia (Fig. 8), and in Cases 5 and 40 the duration of the QRS interval was temporarily increased. In other instances of tachycardia, however, there was normal intraventricular conduction.

Bundle branch block may be transient even when septal infarction is present. The inflammatory reaction and edema surrounding the infarct may diminish after several days, and the bundle branches involved by this process may regain their conductivity. Similarly, collateral circulation from the other coronary artery may establish itself and restore normal conduction. Of interest in this regard are the clinical observations made in Case 7, in which the bundle branch block was abolished temporarily by the intravenous injection of aminophyllin, probably as a result of transient dilatation of the surrounding patent coronary vessels, with improvement in circulation to the conduction system. When collateral circulation was permanently improved within a few weeks, the bundle branch block disappeared spontaneously.

The Effect of the Vagus on Intraventricular Conduction.—Auriculoventricular conduction disturbances due to vagal influences are observed frequently. Whether the latter may also affect conduction through the bundle branches is not entirely clear. Although functional bundle branch block due to vagal stimulation has been reported,[5, 7, 88] it has been stated[89] that intraventricular conduction is not influenced by the vagus nerve. The circulatory factors in coronary occlusion are so evident that vagal stimulation need not be invoked as an explanation for the production of bundle branch block even when the latter is only transient. Were the vagus nerve important, abolishing its action with atropin should decrease the conduction defect. In three cases in which 1/50 gr. of atropin was administered intravenously, the conduction defect was unaffected although the P-R interval was definitely shortened.

The Importance of Cardiac Enlargement in Bundle Branch Block.—We have seen that cardiac hypertrophy was present in every autopsy case with intraventricular block, the majority of hearts weighing 500 gm. or more, and the average weight being 505 gm. Furthermore, we

have found[57] the degree of cardiac enlargement in bundle branch block without myocardial infarction to be even more marked, the average cardiac weight being 660 gm. This suggests a relationship between cardiac enlargement and bundle branch block, particularly since in a large heart without a bundle branch lesion the electrocardiographic configuration not infrequently approaches that of bundle branch block. In coronary occlusion, however, bundle branch block would seem to depend chiefly on the presence of septal infarction. Thus large hearts were observed without conduction defects and, conversely, bundle branch block occurred occasionally when there was little enlargement (Table I). Furthermore, were heart size a factor, one would expect left bundle branch block almost exclusively to have occurred, because of the high incidence of antecedent hypertension and left ventricular enlargement; yet in our series right bundle branch block was frequent. Nevertheless, it may be that a large heart predisposes to the development of bundle branch block in the presence of myocardial infarction or ischemia.

Involvement of a bundle branch usually influences the electrocardiogram differently than cardiac enlargement. Marked widening, notching and slurring of the QRS, with high voltage, seem to be caused by the former, whereas high voltage without widening may result from enlargement alone.

TREATMENT

The treatment of coronary artery occlusion with bundle branch or marked intraventricular block does not differ from the treatment of coronary occlusion in general. Our regime has been described in detail in previous publications,[43, 90, 91] and consists essentially of complete physical and mental rest, good nursing, prevention of gastrocardiac reflexes and lowering of the body metabolism by a low caloric diet, and sufficient sedatives and analgesics to control apprehension and pain. The therapy of congestive heart failure is especially important because of its high incidence in the cases with bundle branch block and because the failure may increase the anoxemia of the conduction system. Emphasis is to be placed on such measures as diminished fluid intake, low calory diet, oxygen administration and mercurial diuretic drugs in conjunction with acidifying salts. Oxygen therapy, particularly, has been found beneficial for defective intraventricular conduction associated with tachycardia[86] and heart failure.[83]

We avoid the use of digitalis in coronary artery occlusion, particularly early in the attack, even when congestive heart failure is present, for we believe that in the presence of acute infarction it may be toxic in ordinary therapeutic doses.[40, 91] We resort to its use only when other measures for the treatment of heart failure have failed.

Quinidine sulphate has been advocated in coronary occlusion to prevent ventricular tachycardia. Septal infarction, which has been shown

to be the underlying pathologic basis for bundle branch block, has also been thought to be the cause of ventricular tachycardia.[27, 34, 53] The septal infarction may either block conduction through the bundle branches or set up an irritative focus leading to ventricular tachycardia. Theoretically, therefore, quinidine would be indicated in cases of coronary artery occlusion with bundle branch block as a prophylactic measure against ventricular tachycardia. Practically these considerations do not hold true, for as we have seen previously, in only 2 of our 56 cases was there ventricular tachycardia, and only four instances of the latter were observed in the 375 cases of coronary occlusion.[40] Such a small incidence does not warrant the routine prophylactic administration of quinidine. Furthermore, experimental studies[92-94] have shown that quinidine in therapeutic doses depresses intraventricular conduction and in toxic doses may cause marked intraventricular block. Clinically, also, cases of bundle branch block following quinidine administration have been observed.[95-97] It is possible, therefore, that the use of quinidine in the presence of bundle branch block or intraventricular block may actually increase the degree of conduction defect.

A drug which should be used more frequently in the acute stage of coronary artery occlusion is aminophyllin, administered intravenously. Its use in two of our patients deserves special mention. In Case 26, it was a life-saving measure. The patient, a 35-year-old man, suddenly became unconscious on the second day of his attack. The heart rate first slowed to 40 per minute, and then the heart beats became entirely inaudible, and the patient appeared dead. The intravenous injection of 0.24 gm. of aminophyllin at this point caused a sudden revival of the patient. Following a transient seizure of auricular tachycardia with left bundle branch block, permanent right bundle branch block appeared (Fig. 8). The patient recovered and is alive and well today. The presence of both left and right bundle branch block in rapid succession suggests that a possible cause of the syncope was an Adams-Stokes seizure due to bilateral bundle branch block, which was lifted by the transient improvement in coronary blood flow following the injection of aminophyllin. In Case 7 we were successful in abolishing left bundle branch block temporarily by the intravenous injection of this drug. By improving the collateral circulation to the infarct and the area surrounding it, aminophyllin may hasten the return of normal conduction in the transient types of bundle branch block following coronary artery occlusion.

SUMMARY

1. Intraventricular block, including bundle branch block, was present in 15 per cent of 375 cases of acute coronary artery occlusion.

2. Patients in this group were older than controls and presented clinical and pathologic evidence of severe heart disease. Congestive

heart failure, antecedent hypertension, cardiac enlargement and evidence of previous attacks were the rule.

3. The conduction defect was usually observed on the first day and was usually permanent. In six patients it was transient.

4. Intraventricular or bundle branch block could not be diagnosed clinically since there were no specific symptoms or physical signs. Gallop rhythm was present in 60 per cent of the cases, but was probably due to the associated severe heart failure.

5. Left bundle branch block occurred in 51 per cent of the group, typical or atypical right bundle branch block in 28 per cent and intraventricular block in 21 per cent. The configuration of the ventricular complexes as well as the axis deviation often varied in serial records.

6. In the presence of intraventricular block characteristic electrocardiographic signs of myocardial infarction failed to appear in one-third of the cases.

7. The precordial lead may be of diagnostic importance, for progressive S-T and T-wave changes may occur only in this lead. Absence or marked diminution in the initial positive deflection in this lead is usually due to anterior wall infarction even when bundle branch block is present, although occasionally the latter alone is the cause.

8. Intraventricular block was often associated with impaired auriculoventricular conduction. Other arrhythmias were not more common than in coronary occlusion in general.

9. The sudden appearance of defective intraventricular conduction should suggest recent coronary occlusion. Since bundle branch or intraventricular block following coronary occlusion is usually permanent. it may be the only evidence that the patient has suffered a coronary occlusion in the past. Repeated attacks of coronary occlusion may result in a progressive increase in the QRS duration.

10. The presence of defective intraventricular conduction in coronary occlusion adds to the seriousness of the prognosis, the mortality rate being 42 per cent. The more severe the conduction defect was, the higher the mortality rate, but there was no correlation with the type of block.

11. The anatomical basis for the conduction defect was septal infarction, which was present in four-fifths of the hearts.

12. Correlation between the vessels occluded or the location of the septal infarct and the type of conduction defect could not be made; occlusion of the right coronary artery was as frequent as that of the left and anterior infarction was as common as posterior infarction, regardless of the type of block.

13. The persistence of normal conduction in many cases with septal infarction was attributed mainly to the presence of adequate collateral circulation in the septum.

14. Transient bundle branch block was probably due to anoxemia resulting from shock, tachycardia, and heart failure.

15. The vagus nerve probably played no role in bundle branch block since the latter was not affected by the injection of atropine.

16. The relation between cardiac enlargement and bundle branch block was discussed, and the influence on the electrocardiogram of cardiac enlargement and bundle branch involvement contrasted.

17. The treatment is that of coronary occlusion in general, with special attention to heart failure. The value of aminophyllin and oxygen was emphasized. Quinidine and digitalis should be used only when there is persistent rapid ventricular rate with failure.

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THE FORM OF THE ELECTROCARDIOGRAM IN EXPERIMENTAL MYOCARDIAL INFARCTION*

V. The Later Effects Produced by Ligation of the Right Coronary Artery†

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PREVIOUS articles of this series have dealt with the form of the ventricular complex in direct and semidirect leads from the epicardial surface of infarcts produced by ligation of the anterior descending branch of the left coronary artery.[2-4] This procedure leads to massive infarction of the anterior wall of the left ventricle. As a rule those portions of the anterior wall of the right ventricle which are close to the septum are involved to some extent, but here the infarction is usually patchy, and the boundaries of the areas affected are not as a rule clearly discernible. In order to determine whether direct and semidirect leads from the surface of right ventricular infarcts yield curves similar to those obtained from the surface of left ventricular infarcts, it was, therefore, necessary to study infarcts of the kind produced by ligation of the right coronary artery. These infarcts are confined to the wall of the right ventricle and are as a rule large, conspicuous, and sharply outlined. It is the purpose of this article to describe the observations made upon infarcts of this type.

As in the experiments described in earlier articles, the ligation was performed under aseptic conditions, and the chest wall was completely restored. If the animal survived this initial operation, an electrocardiographic study was made at a later date, when the chest was reopened and the anterior surface of the heart was explored by means of direct and semidirect leads. These leads were taken with a vacuum tube in the string-galvanometer circuit, and the connections were so made that negativity of the exploring electrode produced an upward deflection in the finished record. For direct leads the galvanometer sensitivity was reduced to one-twentieth normal; for semidirect leads it was reduced to three-twentieths normal. Standard Lead I was recorded simultaneously with these special leads and is represented by the upper trace in all of the curves reproduced. Two kinds of exploring electrodes were employed. For ordinary epicardial leads we used a soft-tipped electrode of the type described in a previous article.[8] For leads from the ventricular cavities and for the purpose of determining whether the subepicardial

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†For previous articles of this series see Wilson, Hill, and Johnston[1-3] and Johnston, Hill, and Wilson.[4] The observations reported in this article were briefly described in a paper read at a meeting of the Association of American Physicians.[5] See also Wilson et al.[6-8]

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muscle in a given region was living or dead we made use of a short length of enameled copper wire sharpened at one end where the insulation was scraped off for a distance of 1 or 2 mm. The nature of the curves obtained from living and from dead muscle when such an electrode is employed has been discussed elsewhere.[3, 4, 8] The exploring electrode was paired with an electrode of similar construction in contact with the subcutaneous tissues of the left hindleg.

Ligation of the right coronary artery in the dog seems somewhat less likely to prove immediately fatal than ligation of the anterior descending branch of the left. In the seven experiments which we performed, the ligatures were placed about that part of the vessel which lies close to the junction of the right auricular appendage with the main body of the right auricle. One animal died about one hour after the ligatures were tied. In three instances the ligatures were improperly placed and the main stem of the artery was not occluded. In two of these experiments small infarcts, due to obstruction of one of its branches, were produced. The three remaining ligations were entirely successful, and large infarcts resulted, but one animal died when the chest was reopened at the time of the second operation, so that the electrocardiographic study could not be completed.

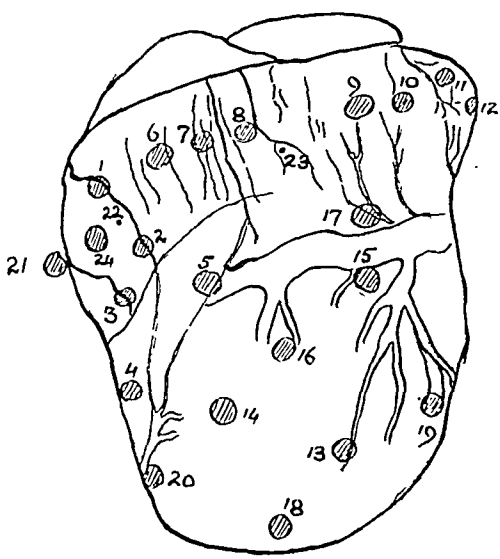

Fig. 1.—Experiment 1 (Dog 38). Outline drawing of the anterior surface of the heart showing the location of the points from which direct leads were taken.

ILLUSTRATIVE EXPERIMENTS

Experiment 1 (Dog 38).—In this instance the electrocardiographic studies were made five days after ligation of the right coronary artery. The standard electrocardiogram taken before the chest was opened shows no Q deflections in any lead but is not unusual in other respects. Three precordial leads were taken. For this purpose small copper disks were sewed beneath the skin along a line extending from the right upper to the left lower part of the precordial region. This line crossed the mid-sternal line 12 cm. below the episternal notch. The first disk was 6.5 cm. to the right of the midline, the second in the midline, and the third 7.5 cm. to the left of the midline. Each disk was paired in turn with a similar disk fastened beneath the skin of the left hindleg. In the first of these precordial curves the QRS complex shows no trace of an

initial downward deflection and closely resembles the initial ventricular deflections recorded in direct leads from the infarcted region. The other two curves display a conspicuous deflection of this kind and are not abnormal.

When the heart was exposed, a trapezoidal area of infarction involving the right anterolateral wall of the right ventricle was clearly visible.

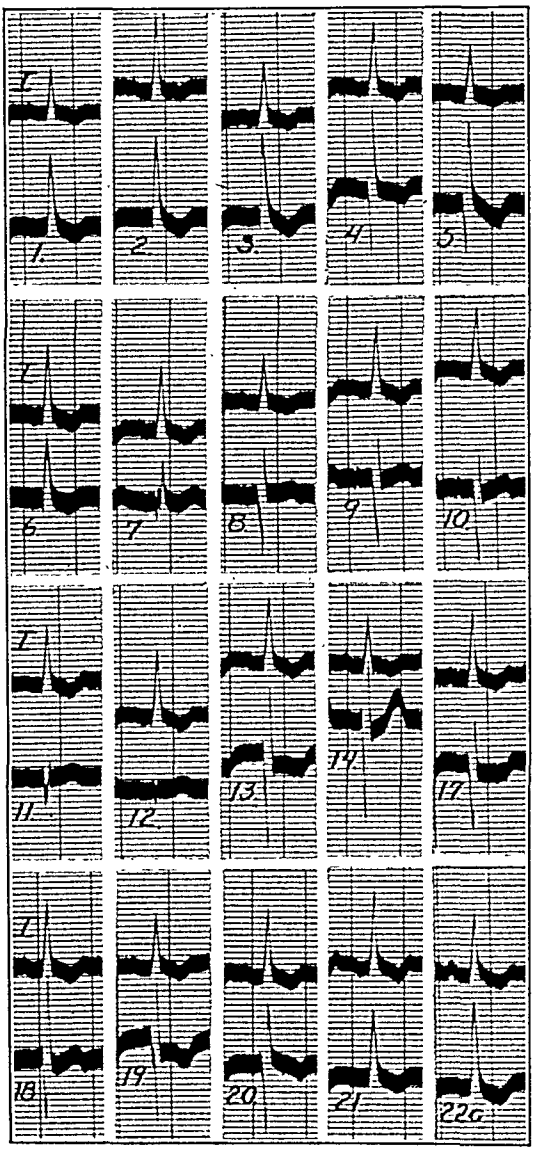

Fig. 2.—Experiment 1 (Dog 38). Direct leads from points marked with corresponding numbers in Fig. 1. The letter *C* indicates that a sharp electrode was employed and was pushed through the ventricular wall so that its uninsulated point was in the ventricular cavity. The upper curve in all records is standard Lead I. In the direct leads relative negativity of the exploring electrode is represented by an upward deflection, and a deflection of 1 cm. represents a potential difference of 20 mv.

The points from which direct leads were taken are indicated on an outline drawing of the heart reproduced in Fig. 1. Many of the curves obtained are shown in Fig. 2. The curves from points 4, 5, 8, 9, 10, 11,

13, 14, 15, 16, 17, 18, 19, and 20, which were outside the boundaries of the infarcted region, all show a prominent initial downward deflection followed by a sharp intrinsic upstroke. Two of these curves, those from points 15 and 16, show definite downward displacement of the RS-T junction indicating very recent injury to the muscle. We attribute this injury to the pressure exerted by the exploring electrode upon the superficial layers of muscle. Accidental disturbances of this kind are frequent when a small electrode is pressed against the beating heart. The deflections of the lead from point 12 are extremely small, apparently because this point lay beyond the pulmonary valves and was not upon cardiac muscle.

In the curves from points 1 and 21 the ventricular complexes consist of a single large upright spike followed by a small U-shaped T deflection and are similar in every respect to those obtained from the surface of left ventricular infarcts which extended completely through the heart wall.[2, 3] The curves from points 2 and 3 differ in one respect only; they show a mere trace of an initial downward deflection. In the curve from point 6 this downward movement is somewhat larger. These points were definitely within the boundaries of the infarcted region. The curve from point 7, which lay very close to the margin of the infarct, may be compared with that from point 8, which was nearby but upon healthy muscle. In the latter there is a deep initial downward deflection followed by an intrinsic deflection of large amplitude; in the former both the initial downward movement and the intrinsic deflection are small, and the intrinsic upstroke is conspicuously notched. The curve obtained by thrusting a sharp electrode through the ventricular wall at point 22 is hardly distinguishable from those obtained from the surface of the infarct at points 1 and 21. The same may be said of the curve recorded when the stab electrode was thrust through the ventricular wall at point 23.

After the curves which have been described had been taken, we attempted to cut the right branch of the bundle of His. This structure was injured but not completely severed, and partial bundle branch block resulted. Standard Leads I and III taken immediately after the cut was made are shown in Fig. 3 *A*. It will be noted that in this tracing ventricular complexes depicting right branch block alternate with complexes of more normal outline. Later the injured bundle passed only an occasional impulse (Fig. 3 *B*). The curve obtained at this time by leading from the epicardial surface at point 24 with a soft-tipped electrode (Fig. 3 *B*) and that obtained by leading from the ventricular cavity at point 22 with the stab electrode (3 *C*) are indistinguishable. It should be emphasized that in both these curves the branch block complexes begin with a large downward deflection, which we attribute to electrical forces generated by the excitatory process in its spread through

the ventricular septum from left to right. The initial deflection of the QRS complexes inscribed when the right bundle branch functioned in the normal way is in the upward or minus direction.

Dr. C. V. Weller was good enough to prepare and examine sections of a large block of tissue removed from the infarcted area. He reported that the heart muscle in this region showed patchy necrobiotic alteration and areas of early fibroblastic proliferation. Leucocytic infiltrations were seen at the margins of the ischemic regions.

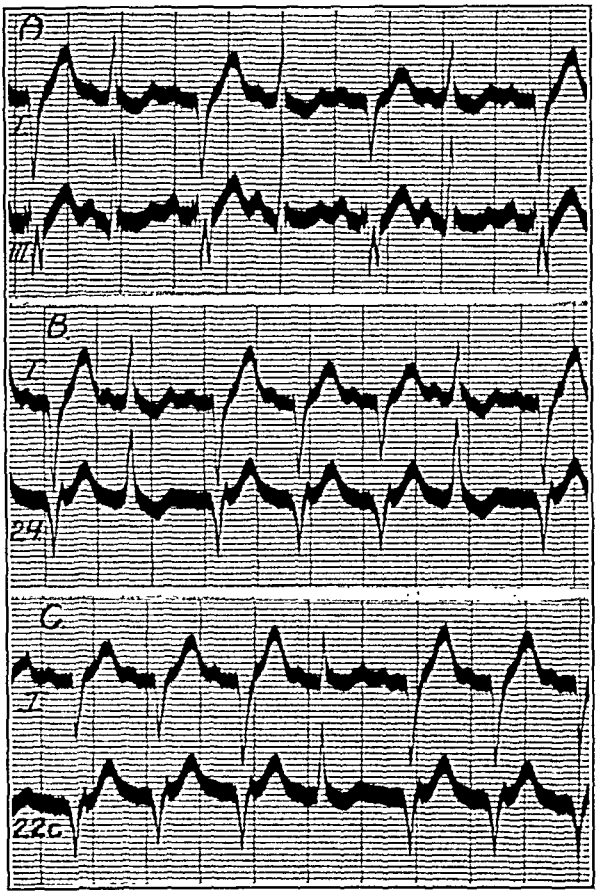

Fig. 3.—Experiment 1 (Dog 38). A.—Standard Leads I and III after attempt to cut the right branch of the His bundle. Partial right bundle branch block is present. B.—Standard Lead I (above) and a direct lead from point 24, taken with the ordinary soft-tipped electrode. C.—Standard Lead I (above) and a direct lead from the right ventricular cavity obtained by thrusting a sharp electrode through the ventricular wall at point 22. For the location of these points see Fig. 7.

Experiment 2 (Dog 42).—In this instance the electrocardiographic study was made two days after ligation of the right coronary artery. The standard electrocardiogram taken before the chest was opened is not obviously abnormal. Three precordial leads were also taken; one from a disk 5 cm. to the right of the midline; one from a disk in the midline 12.5 cm. from the episternal notch; and one from a disk 7.5 cm. to the left of the midline. The three disks were sewed beneath the skin and were arranged along a line extending from the right upper to the left

lower part of the precordium. These leads show no unequivocal signs of myocardial infarction, but in the first two the preintrinsic downward

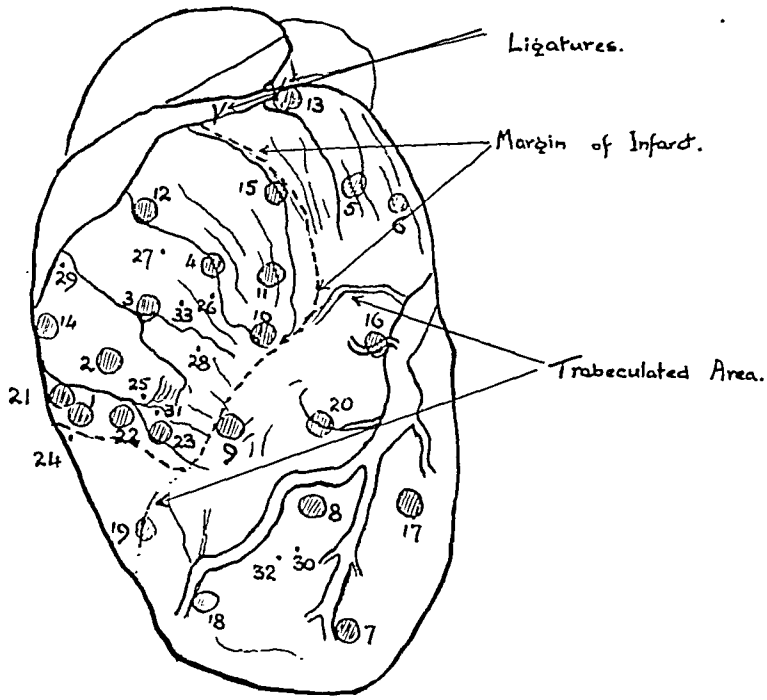

Fig. 4.—Experiment 2 (Dog 42). Outline drawing showing the location of the points from which direct leads were taken. The dotted line marks the approximate boundaries of the infarct.

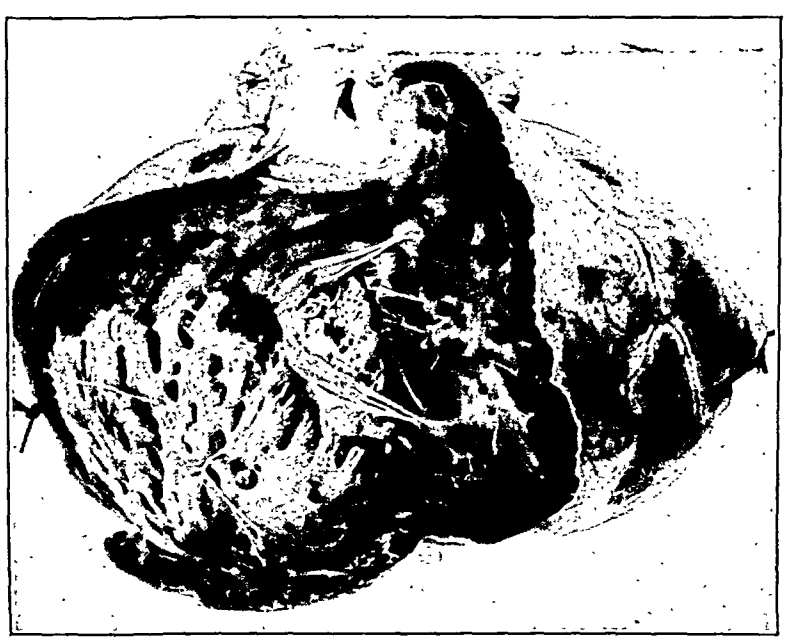

Fig. 5.—Experiment 2 (Dog 42). Photograph of the endocardial surface of the infarcted region.

deflection is unusually small. When the heart was exposed the infarct was clearly seen but its margins were not very sharply defined. An outline drawing of the heart which shows where the ligatures were placed

and the location of the infarcted area is shown in Fig. 4. The points explored by means of direct leads are indicated on this sketch. A photograph of the endocardial surface of the infarcted region is reproduced in Fig. 5. A large number of the curves obtained appear in Fig. 6.

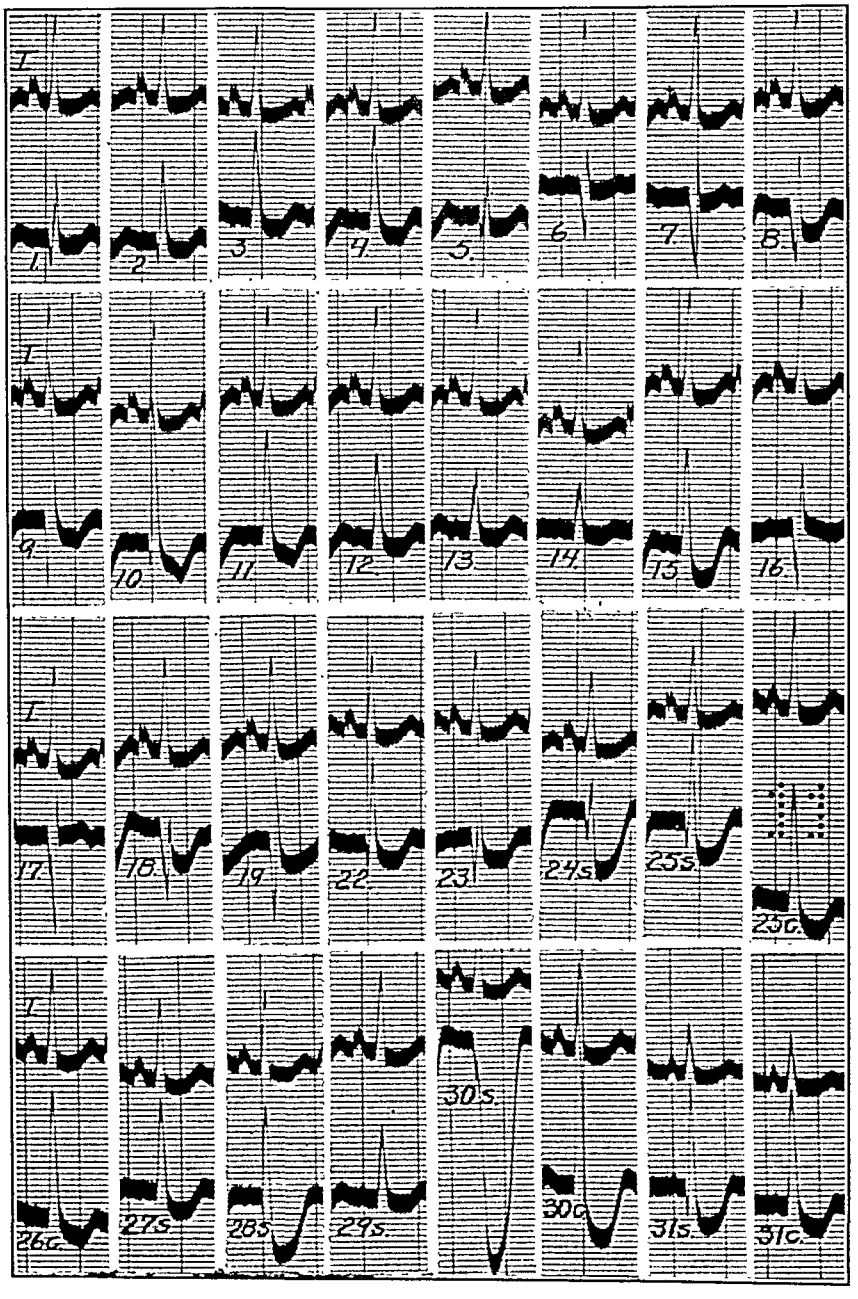

Fig. 6.—Direct leads from the points bearing corresponding numbers in Fig. 4. The upper curve of each record is standard Lead I. The letter *S* indicates that a sharp electrode was used and was pressed against the epicardial surface. The letter *C* indicates that the sharp electrode was thrust through the ventricular wall into the ventricular cavity. In the direct leads relative negativity of the exploring electrode is represented by an upward deflection and a deflection of 1 cm. represents a potential difference of 20 mv.

The direct leads from points 5, 6, 7, 8, 9, 16, 17, 18, 19, and 20, which were definitely outside the boundaries of the infarcted area, all show QRS complexes which begin with a deep initial downward deflection and display an intrinsic deflection of large amplitude. These complexes are of the kind usually obtained when the heart is normal. In the leads from points 8, 18, and 20 there is some downward displacement of the RS-T junction which we attribute to injury to the subepicardial muscle produced by pressing the exploring electrode too firmly against the heart. The curve from point 13, which is also outside the infarcted region, lacks both an initial downward deflection and a definite intrinsic deflection. In this instance we believe that the electrode must have been placed too high so that it rested upon the nonmuscular tissue of the auriculoventricular groove.

The leads from points 4, 11, 12, 14, and 15 yielded ventricular complexes consisting of a single large upright spike followed by a U-shaped T deflection. These complexes differ in no way from those which, in other experiments, occurred in leads from the surface of infarcts extending completely through the wall of the left ventricle.

The curves from points 3 and 21 are similar to those described in the preceding paragraph but show a trace of an initial downward movement preceding the large upward deflection. In the curves from points 1, 2, and 22 this initial downward deflection is larger and in the curves from points 10 and 23 it is still larger and not definitely subnormal in size.

We may now consider the curves obtained by using the sharp stab electrode. Leads from the right ventricular cavity were taken by thrusting this electrode through the ventricular wall at points 26, 27, and 31. These curves closely resemble those obtained from the epicardial surface at points 4, 11, 12 and 15 with the ordinary soft-tipped electrode. The deflections of the lead from the left ventricular cavity taken by forcing the stab electrode through the wall at point 30 are of similar outline but of much larger size. No trace of an initial downward or plus deflection is present in any of these curves. When the sharp electrode was pressed against the epicardial surface of the left ventricle at point 30, a monophasic ventricular complex was recorded. At points 27 and 29, which were on the infarcted region, the same procedure yielded curves no different from those obtained with a soft electrode at neighboring points. The absence of RS-T displacement in these leads indicates that at these two points the ventricular wall was dead. The two curves obtained with the sharp electrode from the epicardial surface at points 25 and 31 are almost identical. Unlike those from the ventricular cavity at the same points, they display a distinct initial downward deflection. They differ from the cavity curves also as regards the level of the RS-T junction and the depth of the U-shaped T deflection. The first of these differences must be ascribed to electrical forces generated by the outward spread of the excitatory process and hence to the presence of living

muscle in this part of the ventricular wall. The second difference must be attributed to injury sustained by this muscle when the sharp electrode was pressed against it. The curves obtained with the stab electrode at points 24 and 28 show still greater RS-T displacement, which indicates that in these regions also the ventricular wall contained living muscle.

After the leads described had been taken an attempt was made to cut the right branch of the bundle of His. Ventricular complexes characteristic of canine right branch block were recorded immediately afterward, although subsequent examination failed to reveal a cut definitely transecting the bundle branch. After bundle branch block had been produced a lead from the right ventricular cavity at point 33 and a surface lead from the same point (Fig. 7) yielded ventricular complexes identical in form, which began with a prominent initial downward deflection. Post-mortem examination revealed that in the neighborhood of points 1, 22, 23, 25, and 31 the infarction was distinctly patchy, whereas in the neighborhood of points 3, 4, and 27 the ventricular wall appeared to be uniformly involved. Microscopic examination of several blocks of

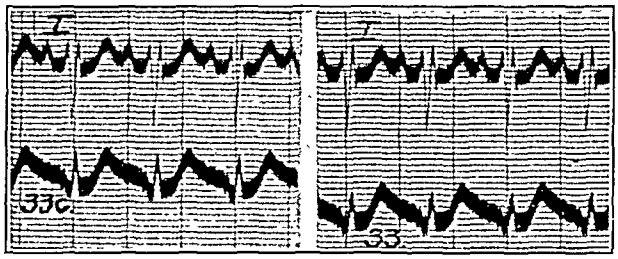

Fig. 7.—Experiment 2 (Dog 42). Curves taken after attempt to cut the right branch of the His bundle. Right bundle branch block is present. The upper curve in each record is standard Lead I. The lower curve on the left was obtained by thrusting the sharp electrode through the ventricular wall at point 33. The lower curve on the right was obtained from the epicardial surface at the same point with the ordinary soft-tipped electrode.

tissue removed from the infarcted region showed areas of simple necrosis and of necrobiosis with active leucocytic infiltration. Beneath the endocardium and around the blood vessels there was early calcification. In certain areas the process extended completely through the wall, although it appeared more marked on the endocardial side (Dr. Weller).

COMMENTS

The observations described demonstrate that direct leads from the outer surface of an infarct which involves the whole thickness of the right ventricular wall yield ventricular complexes of the same form as those seen in direct leads from the surface of an infarct which extends completely through the left ventricular wall. In the case of infarcts of the former as in the case of infarcts of the latter kind, leads from the epicardial surface and leads from the adjacent portion of the ventricular cavity yield curves that are practically identical when the ventricular wall contains no muscle capable of responding to the excitatory

process. This is true not only when the potential of the ventricular cavity is negative throughout the QRS interval, as is normally the case, but also when the potential variations of the ventricular cavity are altered by section of the bundle branch which supplies the infarcted ventricle. The effect of bundle branch block upon the potential variations of the homolateral and contralateral ventricular cavities has been discussed in a previous article. It should be emphasized that when the infarcted ventricle is activated later than its fellow, the QRS complex of direct and semidirect leads from the infarcted region begins with a plus deflection and not with a minus deflection. Infarction of the left ventricle cannot be expected to lead to disappearance of the preintrinsic plus deflection of the QRS complex of precordial leads if left bundle branch block is present.

In those experiments in which the right coronary artery was ligated, striking changes in the T deflection of direct leads from the margins of the infarcted region were not recorded, possibly because the electrocardiographic studies were not made at the proper time. The changes of this kind observed following ligation of the anterior descending branch of the left coronary artery were never found more than twenty-four hours after this operation. All of the right ventricular infarcts explored were at least forty-eight hours old.

Certain differences between the curves obtained from parts of right ventricular infarcts where some muscle was still capable of responding to the excitatory process and those obtained from parts of left ventricular infarcts which contained living muscle should be noted. In the case of the thick-walled left ventricle the infarct ordinarily involved a much larger area on the endocardial than on the epicardial surface. Direct leads from regions where only the inner layers of muscle were dead yielded curves of a distinctive type in which the QRS complex consisted of an abnormally large initial upward or minus deflection followed by a preintrinsic downward deflection and an intrinsic upstroke, both of subnormal voltage.[3] Curves of this kind were not obtained from the right ventricle. In the case of this relatively thin-walled chamber the boundaries of the epicardial aspect of the infarct were the same as the boundaries of its endocardial aspect in all the animals studied. In both of the experiments described an abnormally small preintrinsic downward or plus deflection occurred in direct leads from certain parts of the infarcted region. Since this deflection was not present in leads from the adjacent part of the ventricular cavity it obviously represented electrical forces produced by living muscle in the infarcted ventricular wall. The presence of this living muscle was also disclosed by the appearance of conspicuous RS-T displacement when a sharp electrode was substituted for the ordinary soft-tipped electrode. Theoretically, changes in the QRS complex of the kind in question might be produced either by infarction involving only the outer layers of the ventricular

wall, which would have the same effect as a reduction in the thickness of the muscle, or by a lesion affecting the inner and outer layers to the same extent without killing all of the fibers in either. A lesion of this kind would reduce the voltage developed during activation of the ventricular wall and hence the potential difference between the epicardial and the endocardial surfaces during the QRS interval. Since we could not demonstrate that the infarction was confined to the outer layers of muscle, the second of these two possible interpretations of the observations in question is probably the correct one.

SUMMARY

Infarction of the wall of the canine right ventricle was produced by ligation of the right coronary artery. This operation was carried out aseptically, and the chest wall was restored. After the lapse of a period sufficiently long to cause death of the fatally injured muscle the heart was exposed, and its anterior surface was explored by means of direct leads. A sharp electrode which could be thrust into or through the ventricular wall was used to obtain leads from the ventricular cavities and to determine whether the infarcted ventricular wall contained living muscle.

Direct leads from the outer surface of right ventricular infarcts which extended completely through the right ventricular wall yielded curves of the same kind as those obtained in earlier experiments by leading from the surface of left ventricular infarcts of the same kind. Both before and after section of the right branch of the bundle of His, leads from the surface of the infarct and leads from the neighboring part of the right ventricular cavity gave practically identical results.

In leads from regions where the infarcted right ventricular wall contained living muscle, the preintrinsic plus deflection of the QRS complex was present but abnormally small. In surface leads from regions where the wall contained no living muscle and in leads from the ventricular cavity this deflection was absent when the cardiac mechanism was normal. When right bundle branch block was induced, a prominent initial downward or plus deflection was present, both in cavity and in surface leads.

It has recently been recommended[9] that in taking direct leads of the kind used in this study the galvanometer connections be so made that relative positivity of the exploring electrode is represented by an upward deflection. In the curves reproduced in this article relative negativity of the exploring electrode is represented by an upward deflection.

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THE CARDIAC OUTPUT IN ARTERIAL HYPERTENSION*

Part II. A Study of Arterial Hypertension Produced by Constricting the Renal Arteries in Unanesthetized and Anesthetized (Pentobarbital) Dogs

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THERE have been relatively few studies[1-6] of cardiac output in arterial hypertension, and these have shown variable results. Disagreement has come in part from the use of different methods, but also from differences in manipulation by those who have used the same method. Lack of uniform criteria in the selection of subjects for study has been another source of error. The clinical classification of hypertension has changed rapidly and has not yet reached a point where diagnostic criteria have been clearly established and accepted. Undoubtedly the reported results have included patients of varying types and in different stages of various diseases.

Holman's study[7] of the cardiac output in hypertension, in which he used a single method and the same patients continuously over a period of several years, has not shown that any consistent abnormality characteristic of arterial hypertension exists. Like normal persons, some of the members of this group exhibited different levels of cardiac output. If hypertension is associated with changes in cardiac output, the difference seems to lie within the normal range. Study of individual cases should settle the question, but the opportunity is rarely given to observe the effect on cardiac output of the development or recession of elevated arterial pressure.

Since it is now possible to produce hypertension in dogs (Goldblatt, Lynch, Hanzal and Summerville[8]) and subsequently to relieve it, an experimental approach to the problem is open. Cardiac output methods and normal standards are, furthermore, fairly well understood for dogs. Knowledge is insufficient to decide whether hypertension produced by constricting the renal arteries is identical with any form of hypertension seen in human beings. Sufficient data exist to show some similarity between them.

METHODS

Adult, healthy dogs, with docile dispositions and weights ranging between 10 and 15 kg., were selected. Their cardiac output was measured by the technique based upon the Fick principle described by Marshall.[9] The oxygen consumption was measured with a clinical spirometer, on the tracing of which the respiratory rate was afterward counted. The animals were trained to lie relaxed and quiet on

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TABLE I

DATA ON CARDIAC OUTPUT

DOG	DATE	STATE	OXYGEN CONSUMPTION C.C./MIN.	ARTERIAL BLOOD VOL./%/OXYGEN	VENOUS BLOOD VOL. %	ARTERIOVENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT LITER/MIN.	INDEX LITER/MIN./SQ. M.	BLOOD PRESSURE	RESP. PER MIN.	PULSE RATE PER MIN.	HB. R.B.C.	REMARKS
No. 2	2/ 2/37	Nemb. deep*	80.7	18.84	15.64	32.0	2.5	3.9		4-5	150		
Male	2/24/37	Nemb. deep	82.8	16.67	13.14	35.3	2.3	3.7		3-4			
13.5 kg.	3/ 1/37	Unanest'd	97.5	19.14	13.98	51.6	1.9	3.1	140/90		80		
	3/ 8/37	Unanest'd	92.1	17.06	12.66	44.0	2.1	3.4	146/98		70		
	3/17/37	Nemb. light	99.8	17.80	13.11	46.9	2.1	3.3	144/90	5-8	105		Sick; anemic.
		Renal artery clamp applied—developed hypertension											
	6/ 2/37	Unanest'd	99.9	10.15	3.74	64.1	1.6	2.3	236/170	22	90	61% 4,904,000	
	6/ 4/37	Unanest'd	103.6	9.31	2.95	63.6	1.6	2.6	196/152		100?	4,064,000	Convulsions; died.
No. 4	2/17/37	Nemb. deep	87.2	13.44	9.44	40.0	2.2	3.9		7	130		
Female	5/21/37	Unanest'd	118.8	19.08	14.74	43.4	2.7	4.0	156/100	24			
15 kg.	5/24/37	Unanest'd	115.2	17.61	12.90	47.1	2.4	3.5	130/76	19			
	6/ 8/37	Unanest'd	100.6	19.22	15.10	41.2	2.4	3.4	132/84	16			
	6/10/37	Renal artery clamp applied—developed hypertension											
	6/14/37	Unanest'd	99.8	19.58	14.70	48.8	2.0	2.9	230/162	22			
	6/15/37	Unanest'd	100.3	19.36	15.15	42.1	2.4	3.4	220/156	21			
	6/17/37	Unanest'd	105.2	17.81	13.8	40.1	2.6	3.8	182/124	16			

*Pentobarbital.

TABLE I—CONT'D

No. 5 Male 13.5 kg.	5/24/37	Nemb. deep	90.5	15.29	12.38	29.1	3.1	4.8	136, 122	10	150		Van Leersum loop.
	3/ 8/37	Nemb. light	77.3	15.10	11.03	40.7	1.9	3.0		24	95		
	3/15/37	Nemb. light	75.6	16.83	12.96	38.7	2.0	3.1	148	18	105		
	3/24/37	Renal artery clamp applied—developed hypertension											
									190				Unanest'd;
	3/29/37	Nemb. light	82.7	18.10	13.51	45.9	1.8	2.9	140	20	120		anest'd
No. 8 Female 14 kg.	3/22/37	Nemb. light	69.8	12.79	18.36	44.3	1.6	2.5	150/86	18	90		
	4/ 5/37	Unanest'd	123.2	19.07	12.82	62.5	2.0	3.2	164/94	20	96		
	4/14/37	Unanest'd	87.8	18.36	14.01	43.5	2.0	3.1	110/68				
	4/28/37	Unanest'd	107.2	17.83	11.75	60.8	1.8	2.6	150/80	28	85	74%	
	5/ 5/37	Unanest'd	91.6	19.14	13.95	51.9	1.8	2.6	138/80	24			
	5/ 8/37	Renal artery clamp applied—developed hypertension											
	5/12/37	Unanest'd	99.8	15.73	9.90	58.3	1.7	2.7	196/137	26		82% 5,848,000	
	5/19/37	Unanest'd	87.7	17.15	12.23	49.2	1.8	2.6	216/146	18		86% 7,104,000	
	6/11/37	Unanest'd	78.0	19.19	15.05	41.4	1.9	2.7	126/74	27			
No. 10 Female 16 kg.	5/ 3/37	Anest'd	85.0	15.13	12.91	22.2	3.8	5.6	136/82	18			
	5/10/37	Unanest'd	97.5	15.89	12.04	38.5	2.5	3.6	136/82	22			
	5/14/37	Unanest'd	111.5	16.83	13.25	35.8	3.1	4.2	134/89	22		73%	
	5/19/37	Renal artery clamp applied—developed hypertension											
	6/ 3/37	Unanest'd	114.5	19.26	15.19	40.7	2.8	3.8	213/150	18			
	6/ 9/37	Unanest'd	102.0	20.00	16.57	34.3	2.9	4.0	230/158	23			
	6/21/37	Second renal artery clamp applied—hypertension increased											
	6/23/37	Unanest'd	116.6	19.85	15.05	48.0	2.4	3.2	260/190				
	6/30/37	Unanest'd	115.0	21.91	17.45	44.6	2.6	3.5	230/160	20			
No. 11 Female 14.5 kg.	4/30/37	Nemb. light	84.0	14.09	9.80	42.9	2.0	3.2	160/90	20	90		
	5/10/37	Unanest'd	102.1	16.08	10.34	57.4	1.8	2.8	168/104	22	84		
	6/ 1/37	Unanest'd	110.7	16.50	10.89	56.1	2.0	2.9	164/108	20	80		
	6/ 3/37	Renal artery clamp applied—developed hypertension											
	6/ 7/37	Unanest'd	112.9	15.82	10.78	50.4	2.2	3.0	180/120	30			
	6/11/37	Second renal artery clamp applied—hypertension increased											
	6/14/37	Unanest'd	94.3	12.69	8.00	46.9	2.0	3.0	208/140	26			
	6/16/37	Unanest'd	102.5	12.35	8.02	43.3	2.3	3.4	200/138				
	6/30/37	Unanest'd	99.8	16.35	10.26	60.9	1.6	2.6	188/130	20			

their left sides. An airtight connection between the apparatus and the dogs' muzzles was made by the Blalock mask,[10] the efficiency of which was readily tested by increasing the pressure within the circuit once or twice during the test period. With the chest wall carefully anesthetized by novocain and with the animal turned gently upon its back, samples of mixed venous blood and arterial blood were taken by direct puncture from the right and left ventricles, in the order named. Occasional arterial samples were drawn from a femoral artery. The dogs were not disturbed by the procedure unless a rib was struck or the pericardium was scraped or pulled.

Samples of blood were collected under mercury in oxalated ice-cold glass tonometers. Their oxygen content was analyzed in duplicate, within one hour, by the Sendroy modification[11] of the Van Slyke[12] method. They were kept on ice in the interval.

The surface area used in calculating the cardiac output index was estimated by the Meeh-Rubner formula,[13] which is believed to be sufficiently accurate because the dogs used were similar to each other in size and state of nutrition.

Systolic and diastolic blood pressures were taken by auscultation with a small bell over the dorsalis pedis artery while the dogs lay quietly on their sides. In one dog (No. 5) a van Leersum carotid loop had been prepared. Numerous blood pressure readings were made, but only one representative set of figures was recorded for each test. The pulse rate counts were similarly condensed.

The dogs fasted from four o'clock of an afternoon until the experiments were performed about twenty-four hours later. They rested on the table for at least fifteen minutes. Measurements of the cardiac output of each animal were made at intervals until satisfactory uniform values were established to serve as controls. The operation for bringing on arterial hypertension was then undertaken, and, as soon as the animal recovered and hypertension became established, the observations were repeated. A well-trained dog behaved as well after operation as before. In one instance (dog No. 8) observations were continued after spontaneous return of the blood pressure to normal. In order to maintain body weight and normal hemoglobin in the red blood cells the dogs were given generous diets, including raw meat and, sometimes, iron. The red cells were counted in the standard chamber, and hemoglobin was estimated with the Sahli hemoglobinometer. Slight degrees of postoperative anemia disappeared promptly except in dog No. 2, which grew steadily more ill and finally died in a state of clonic convulsions, the blood urea nitrogen being 136 mg. per cent.

Some observations were made on cardiac output under the influence of general anesthesia. Pentobarbital (nembutal) was given intravenously in doses of 15 to 35 mg. per kilogram of body weight. The size of the dose depended upon the depth of anesthesia that was desired. Doses close to the minimum or maximum amounts were usually injected, and the states of anesthesia were described as either "light" or "deep."

RESULTS

Six dogs were studied before and after arterial hypertension was established (Table I). Of these, one (No. 5) was observed solely under the influence of general anesthesia, and the results in another (No. 2) were invalidated by the poor condition of the animal after operation. The effect of arterial hypertension upon the cardiac output was judged, therefore, from the results with four dogs, Nos. 4, 8, 10, and 11 (Fig. 1). Well-marked arterial hypertension developed in all instances, but the pressure was higher in some than in others. Since there was no apparent

change in cardiac output during even the most marked hypertension (No. 10), there was no occasion for attempting a correlation with any particular blood pressure level. As in human beings, the variations in

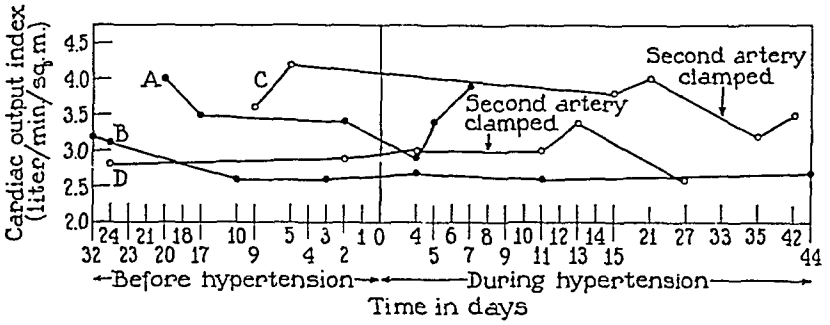

Fig. 1.—The cardiac output expressed as the cardiac index of four unanesthetized dogs is plotted before and during arterial hypertension induced by constriction of the renal arteries. The ordinates show the cardiac index; the abscissas, time in days. Zero abscissa is the time of the first operative procedure. Subsequent operations are shown by arrows. Reading to left and right of zero are observations during normal and hypertensive states, respectively. Line A represents dog No. 4; line B, dog No. 8; line C, dog No. 10; and line D, dog No. 11 (See Table I). The index of each animal is fairly constant; repeated measurements tend to be closer to each other (i.e., their own average) than to the average of a group. The output values for the group and for any individual are not different during hypertension from what they were before it was produced.

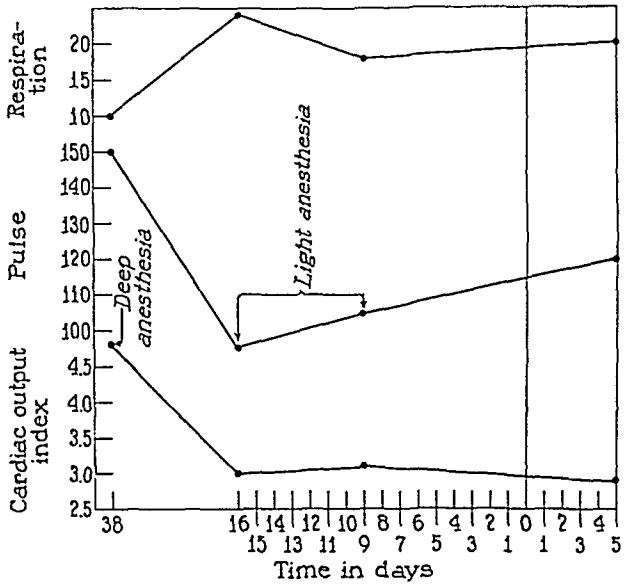

Fig. 2.—The cardiac output expressed as the cardiac index of a single dog (No. 5) is plotted under general anesthesia (pentobarbital), before and after establishing arterial hypertension by means of constriction of the renal arteries. Ordinates and abscissas are as in Fig. 1. In a test under deep anesthesia the cardiac output was greater, the pulse rate was faster, and the respiratory rate was slower than in two subsequent observations under light anesthesia. There was essentially no change in these functions after operation under light anesthesia.

each animal from an accustomed level tended to be smaller than the combined range encountered within a group (Fig. 1).

In dog No. 5, while the animal was under the influence of light pentobarbital anesthesia the cardiac output was the same after the renal artery

was constricted as before (Fig. 2). With this degree of anesthesia the cardiac output was approximately the same as with no anesthesia. Dogs No. 2 and 8 (Table I) exhibited this same phenomenon. The pulse, respiration, and metabolism were essentially undisturbed during light anesthesia (as compared with the values recorded without anesthesia), whereas in deep anesthesia the pulse rate increased, the respiratory rate decreased (Fig. 2), and the metabolic rate was depressed (dogs No. 2 and 4, Table I).

DISCUSSION

The results observed before operation were similar to Marshall's[9] observations on normal unanesthetized dogs. The outputs tended to be higher than 2.2 ± 0.3 liters per minute per square meter body surface, regarded as standard in normal human beings, but the number of observations made in dogs was insufficient to establish comparable figures. To ascertain the normal range lay outside this investigation. Since Starr and Collins[14] have shown that the rate at which blood flows is faster in dogs, the cardiac output may likewise differ. In this study it was necessary only to ascertain how closely repeated measurements agreed. Studies of the animals selected showed that when properly trained and accustomed to the procedure, the output varied less from day to day in individual animals than in the group, and less also when the output was at a low normal level. The fact that the cardiac output is high and that there is greater variation when it is suggests that this phenomenon is related to the dog's temperament and reaction to handling.

Pressure within the arterial system is, as is well known, the resultant, chiefly, of two opposing forces, cardiac output and peripheral resistance. The volume and viscosity of the circulating blood are also factors, but they may be neglected because they have been shown to remain normal in patients with arterial hypertension,[15, 16] and also in dogs with experimental hypertension.[17]

Inasmuch as these studies show that the cardiac output persists unchanged, the high blood pressure could have arisen only through the mechanism of increased peripheral resistance. The same conclusion was reached by Pickering,[18] and by Prinzmetal and Wilson,[19] who found the blood flow in the limbs of patients to be normal. They decided that resistance was increased by means of widespread hypertonus of the arterioles. Their interpretation is supported by the results of these experiments; a normal cardiac output would of course be impossible unless an adequate volume of blood were returned to the heart. It is conceivable that in a late stage of the disease changes in the vessel walls may narrow the vascular bed and result in decrease of the volume of peripheral blood flow, which would in turn diminish the cardiac output. Since the stage studied in these dogs was very early, and since the

outputs were no higher than normal, it seems unlikely that increased output is to be found involved in the mechanism in any stage in the course of arterial hypertension.

To avoid training the dogs, the use of pentobarbital was attempted but was abandoned very soon for two reasons: (1) Under its influence hypertension tended to disappear, and (2) observations of the cardiac output showed unexpectedly large variations. It is known that barbiturate anesthesia tends to lower the human blood pressure, especially in some patients with arterial hypertension. Similarly in these dogs hypertension was undoubtedly interrupted by release of peripheral resistance.

The amount of cardiac output in nonhypertensive dogs under the influence of pentobarbital seems directly proportional to the depth of anesthesia. When it is very light there is no depression of respiration, no tachycardia, no cyanosis, and the cardiac output is equivalent to that found in nonanesthetized animals. There is, in short, no essential disturbance of the circulation. In deeper degrees of anesthesia the respiratory rate fell by at least a half, the total oxygen consumption was reduced, the pulse rate rose, and the cardiac output increased. Since marked cyanosis was present, the fall in the rate of respiration was undoubtedly a result of direct action of the drug upon the respiratory center. Amytal has been reported to depress metabolism[20] and pentobarbital conceivably does so also, since they have similar pharmacologic properties. The increased cardiac output was accompanied by a decrease in the arteriovenous oxygen difference and marked tachycardia. Anoxemia without anesthesia has been shown to produce a similar effect in man[21] and may be credited with a primary etiological role in these dogs.

SUMMARY

1. The cardiac output of healthy unanesthetized dogs under standard conditions varies little from day to day.

2. In several dogs in which the normal range of cardiac output was known, acute arterial hypertension was brought on by constriction of the renal arteries. The cardiac output remained unchanged.

3. Since cardiac output remains unchanged, arterial hypertension seems to depend on peripheral vasohypertonus.

4. A light degree of pentobarbital anesthesia did not change the cardiac output of normal or hypertensive dogs. Anesthesia sufficiently deep to depress metabolism and respiration increased the pulse rate and cardiac output.

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HUMAN AUTONOMIC PHARMACOLOGY*

XVIII. Effects of the Intra-Arterial Injection of Acetylcholine, Acetyl-Beta-Methylcholine Chloride, Epinephrine, and Benzedrine Sulfate

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THE bodily response of man to drugs administered intra-arterially has been investigated by only a few workers. Ellis and Weiss[1] studied the effects of acetylcholine following its administration into the brachial artery, and Battro and Lanari[2] and Allen and Crisler[3] observed the effects of mecholyl and other vasodilator drugs following their intra-arterial administration in normal subjects and in patients with peripheral vascular disease.

This communication reports the effects of the intra-arterial administration of epinephrine, acetyl-beta-methylcholine chloride (mecholyl), acetylcholine and benzedrine sulfate (benzyl methyl carbinamine). If these drugs are given in amounts sufficient to produce a reaction in the tissues supplied by an artery and yet insufficient to reach the general circulation, certain phenomena appear which, because of their localization, can be more directly studied than when these drugs are given intravenously or intramuscularly with the production of general effects. For example, the sweating produced by acetylcholine and mecholyl limits itself to an extremity, and an artificial Raynaud-like reaction brought about by epinephrine can be experimentally produced and more intimately investigated.

MATERIAL AND METHODS

The subjects of this study were for the most part patients suffering from dementia precox. These patients have been the subjects of previous reports[4, 5, 6] from this laboratory and have been repeatedly shown by our present tests to be physiologically normal. The brachial artery was selected because of its accessibility. It was readily punctured by an ordinary 19 to 20 gauge needle over the point of maximal pulsation in the antecubital fossa.

Intra-arterial Administration of Acetylcholine.—Doses of acetylcholine varying from 0.01 mg. to 10 mg., in 0.1 c.c. of water, were injected into the brachial arteries of twelve subjects. Within thirty to sixty seconds following the injection goose flesh appeared on the injected arm, then mild to marked flushing, followed immediately by a variable degree of sweating over the hand and arm, extending to an area slightly above the

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antecubital fossa. The flushing was usually so distinct that the distribution of the brachial arterial tree was sharply outlined. Associated with the above reaction there was increased warmth of the hand and arm. The reaction reached its height in a few minutes and gradually subsided, disappearing in from three to ten minutes, depending on the dose and sensitivity of the patient. In none of the cases in which the smaller doses were used was there any flushing and sweating except in the injected extremity. When the larger doses were used the systemic blood pressure rose slightly, usually no more than 15 mm. Hg. In one case the blood pressure rose 30 mm. Hg, and in another case there was a slight fall in blood pressure. Following the injection of the smaller doses there was no change in systemic blood pressure. With doses ranging from 3 to 10 mg. a moderate rise in blood pressure occurred in the injected arm. With the minimal doses, flushing alone or flushing associated with mild sweating in the injected arm occurred.

Intra-Arterial Administration of Mecholyl.—(1) Mecholyl in doses of 0.1 mg. to 3 mg. in 0.1 c.c. of water was injected into the brachial arteries of nine subjects. Reactions similar to but correspondingly more marked than those obtained by acetylcholine occurred. A local reaction extending from slightly above the antecubital fossa to the end of the fingers occurred almost immediately following the injection, gradually subsiding in from five to ten minutes. Following the administration of the larger doses (3 mg.), the vasodilatation was extremely marked, and the veins stood out prominently. The diastolic pressure in the injected arm could not be measured because the sounds were still audible, even when the pressure in the cuff reached zero. There was only a slight fall in systolic pressure in either arm. In three cases in which extreme vasodilatation and sweating occurred, a pistol shot sound and a systolic and diastolic murmur were heard over the injected brachial artery (Duroziez's sign), due obviously to the greatly increased rate of blood flow toward the periphery associated with the marked vasodilatation.[7] Although in many instances the dose used was great enough to have caused marked general reactions if it had been given by vein, little, if any, general reaction occurred when the intra-arterial route was used.

(2) In eight cases it was found that the minimal reacting dose was between 0.001 mg. and 0.0001 mg. in 0.1 c.c. of water. With these doses either mild flushing or flushing combined with mild sweating of the hand occurred.

Combined Administration of Mecholyl and Atropine.—In five cases the intrabrachial injection of 0.5 mg. of mecholyl was preceded by the subcutaneous injection of atropine (1.3 mg), the mecholyl being given at the height of the atropine response. In no case were any observable local or general effects of mecholyl noted, showing that the local effects of this drug are inhibited by atropine, just as are all the systemic effects.

Combined Administration of Prostigmin and Mecholyl.—In three cases prostigmin (0.5 mg. intramuscularly) was given ten to 15 minutes

prior to the intrabrachial injection of 0.5 mg. of mecholyl. In two other cases both drugs were given simultaneously in the same dosage by the intrabrachial route. In the latter two cases, and in one of the others, the local reaction was very marked. In these cases a pistol shot sound and a systolic and diastolic murmur developed over the brachial artery, and within one to two minutes after the injection of the drugs sounds could be heard down to zero for several minutes. This reaction had been previously observed with mecholyl in doses not less than 3 mg. Thus, prostigmin definitely enhanced the mecholyl effect, acting in its well-established role as synergist[8] to this drug.

Only a slight change in systolic pressure occurred in the injected arm. The systemic blood pressure remained practically unaffected. Very slight, if any, general flushing or sweating occurred in any of these cases.

Intra-arterial Administration of Epinephrine.—(1) Twenty-four subjects were given epinephrine by the intrabrachial route in doses varying from 0.1 mg. to 0.3 mg. (0.1 c.c. to 0.3 c.c. of a 1:1,000 solution). Within a minute goose flesh appeared over the arm, and this was quickly followed by marked pallor beginning in the fingers and extending to the hand and arm up to the elbow; this was especially marked with the larger amounts, so that the arm and hand appeared blanched. With the increase in pallor the radial pulse became increasingly smaller in volume, so that in many cases it could not be felt, whereas the other radial pulse remained unchanged. Associated with the pallor there was marked coldness of the hand. The local reaction reached its height in a few minutes and gradually receded, usually lasting from ten to twenty minutes, in a few cases somewhat longer. In doses up to 0.1 c.c. of a 1:1,000 solution no effect on the systemic blood pressure or pulse was evident. In doses larger than 0.1 c.c. of a 1:1,000 solution slight elevation in general systemic blood pressure occurred. One subject, a neurotic, described the subjective sensations as follows: Within two minutes following the injection of 0.1 c.c. of a 1:1,000 solution of adrenalin the hand felt numb and the fingers were difficult to extend; there was a stabbing pain in the middle of the palm; the tips of the fingers were painful and the hand felt limp; after three minutes tingling of the finger tips began. These sensations continued for ten more minutes. Thirty minutes after the injection, the hand was still slightly pale.

(2) Since the above doses of epinephrine are far beyond the amount liberated in the limb under physiologic conditions, the same twenty-four subjects were given injections of increasing dilution into the brachial artery until minimal, but still definite, local reactions were obtained. It was found that 0.1 c.c. of a 1:100,000 to 0.1 c.c. of a 1:1,000,000 solution of epinephrine (0.001 to 0.0001 mg.) caused definite pallor of the hand, in some cases accompanied by diminution in volume and force of the

radial pulse. In two instances it seemed that the pallor was preceded by slight vasodilatation of the hand and forearm, but when the experiments on these two subjects were repeated, the initial vasodilatation could not be obtained. In most cases mild pilomotor response preceded and accompanied the pallor of the forearm. Following the suggestion of Fatherree and Allen[9] that vasodilatation must first be produced to study the extremes of sensitivity to epinephrine, the arm and hand of one patient were submerged in hot water until maximal vasodilatation occurred. The intra-arterial injection of 0.1 c.c. of a 1:1,000,000 solution of epinephrine then produced clear-cut, easily observable vasoconstriction of the forearm, hand, and wrist. In this same patient the same amount of epinephrine injected in the other hand, not previously vasodilated, produced no discernible effect.

Difference Between Intra-Arterial Administration of Benzedrine Sulfate and Epinephrine.—The injection of various doses of benzedrine sulfate into the arteries of several subjects produced no demonstrable local effects. The systemic effects, however, were marked and occurred exactly as if the drug had been injected into a vein or subcutaneously. In other words, benzedrine sulfate does not remain localized in the distribution of the artery but passes into the general circulation, so that obviously the drug is not destroyed or fixed in the tissues, such as is the case with epinephrine.

Intra-Arterial Administration of Epinephrine Followed by Mecholyl.—In four cases, 0.1 c.c. to 0.3 c.c. of a 1:1,000 solution of epinephrine (0.1 mg. to 0.3 mg.) was injected into the brachial artery, and at the height of the pallor 3 mg. of mecholyl were injected into the same vessel. Immediately following the latter injection small areas of vasodilatation occurred either over the back of the hand and arm or over the bend of the elbow. This vasodilatation disappeared quickly, to be replaced by the pallor due to the epinephrine. In no case was the mecholyl in the amounts given able to overcome the local response in the fingers. Slight, if any, general systemic reaction occurred in any of these cases.

In two cases prostigmin (0.5 mg. intramuscularly) was administered twenty minutes prior to the injection of 0.1 c.c. of a 1:1,000 solution of epinephrine, which was then immediately followed by an intra-arterial injection of 3 mg. of mecholyl. In one of these cases the epinephrine reaction was replaced by vasodilatation down to the metacarpophalangeal junction with no effect on the fingers, so that there was a sharp demarcation between the redness of the palm and the pallor of the fingers. The vasodilatation gradually spread to the fingers, so that eight minutes following the injection of the mecholyl the fingers became red, leaving that hand much warmer than the opposite hand. There was also a moderate general reaction as shown by a fall in systemic blood pressure, an increase in pulse rate, salivation, tearing, coughing, and sweating of the face and chest. In the other case, although the same doses of the drugs

were used, the marked pallor of the fingers was unaffected by the mecholyl, although moderate vasodilatation of the arm occurred. In two other cases the local responses produced by 0.1 c.c. of a 1:1,000,000 solution of epinephrine were not affected by 3 mg. of mecholyl when both drugs were given simultaneously into the brachial artery.

Intra-Arterial Administration of Mecholyl Followed by Epinephrine.—In five subjects mecholyl was injected into the brachial artery and followed, within one to three minutes, by adrenalin administered into the same vessel. Two of the subjects were given 0.1 mg. of each drug. Although a moderate local response to the mecholyl developed, the epinephrine overcame such a local reaction within one to three minutes, and the final effect was apparently in no way different from that which developed when the latter drug was given alone. In both cases, however, there was a rise in systemic blood pressure of 14 and 28 mm. Hg, respectively. In the other three cases a similar procedure was carried out, using 3 mg. of mecholyl and 0.1 mg. of adrenalin. In one case a moderate local mecholyl reaction was replaced in three minutes by pallor of the same parts. In the other two cases, however, the epinephrine response was definitely delayed, so that pallor occurred in eleven and thirty-three minutes, respectively, following the epinephrine injection. The blood pressure was not followed in the latter three cases.

DISCUSSION

The foregoing experiments indicate that acetylcholine and mecholyl, when given intravenously in dosage sufficient to cause definite general reactions, produce only a local response of the hand and arm on the injected side when administered intra-arterially. Within such dosage the usual absence of a general response indicates that these drugs are destroyed or fixed in the local tissues. Thus, 1 mg. of acetylcholine and 0.1 mg. of mecholyl produce marked vasodilatation of the vessels of the hand and arm without general reaction when injected into the brachial artery. This indicates that both these drugs act peripherally on the muscle cells of the blood vessels and the secretory cells of the sweat glands.

Epinephrine, injected intra-arterially in amounts from 0.1 mg. to 0.001 mg., causes a definite local response, as evidenced by pallor and coldness of the arm and hand, particularly of the fingers, without any systemic response. With the larger doses the pulse becomes smaller in volume and may disappear entirely. In the same subjects amounts as small as 0.0001 mg. produce a local constrictor response. Once a local reaction is established by the smallest effective dose of epinephrine, mecholyl in amounts up to 3 mg. will only partly counteract the epinephrine reaction. These data indicate that the amount of epinephrine sufficient to produce the vasoconstrictive phenomenon of

Raynaud's disease in the extremities must be about 0.001 mg. to 0.0001 mg. Furthermore, since 3 mg. of mecholyl intra-arterially will not replace, or only incompletely replace, the local epinephrine reaction, it would a priori appear doubtful that parasympathomimetic drugs, whether given intra-arterially or by iontophoresis, would be efficacious in the treatment of Raynaud's disease. Doses larger than 3 mg. of mecholyl might counteract the epinephrine reaction but would be likely to produce undesirable or untoward general effects.

Because of the absence or very mild evidence of general reactions, it appears that relatively large amounts of epinephrine are fixed or destroyed in situ when administered intra-arterially. When injected into a vein and distributed throughout the body, there is a general reaction, probably because cells throughout the body are affected.

When mecholyl is given prior to the epinephrine, there may be sufficient local dilatation of the peripheral vessels to allow the latter drug to reach the general circulation. Again, the fact that epinephrine may still cause a local response several minutes after its intra-arterial injection if it has been preceded by large intra-arterial doses of mecholyl indicates that it becomes fixed in the tissues for a relatively long period of time.

SUMMARY AND CONCLUSIONS

Acetylcholine, mecholyl, epinephrine, and benzedrine sulfate in varying amounts were introduced into the brachial artery of man. In some instances combinations of atropine and mecholyl and, in others, prostigmin and mecholyl were similarly injected.

(1) Intra-arterial injections of acetylcholine in amounts varying from a minimal dose of 0.01 mg. to 10 mg. produced a local reaction of the arm and hand, consisting of vasodilatation, pilomotor stimulation, and usually sweating, without any general reaction except a slight rise in general blood pressure following the larger doses.

(2) Intra-arterial injections of mecholyl in amounts varying from 0.0001 mg. to 3 mg. effected similar, although correspondingly more marked, local reactions than acetylcholine, in the larger doses producing a marked change in the local blood pressure. In some cases pistol shot sounds and Duroziez's phenomenon appeared and it became impossible to measure the diastolic pressure. General reactions appeared only in those cases in which more than 2 mg. were used or when the effect was enhanced by prostigmin. Atropine was able to prevent completely the mecholyl reaction.

(3) The minimal intra-arterial effective dose was found to be (a) in the case of acetylcholine 0.01 mg. to 0.1 mg., and (b) in the case of mecholyl 0.0001 mg. to 0.001 mg. Slight or no general reaction occurred following the intra-arterial injection of less than 10 mg. of acetylcholine and less than 2 mg. of mecholyl.

(4) Intra-arterial injections of epinephrine in widely varying doses (0.0001 mg. to 0.3 mg.) produced vasoconstriction of the arm and hand as shown by pallor and coldness in the areas supplied by the brachial arterial tree, a reaction similar in many respects to that seen clinically in Raynaud's disease.

(5) The minimal effective intra-arterial dose of epinephrine was found to be between 0.0001 mg. to 0.001 mg. The tissues of the hand are able to break down comparatively large amounts of epinephrine, as evidenced by the lack of general reaction to a dose below 0.1 mg.

(6) The vasoconstriction produced by epinephrine even in minimal amounts was not completely overcome by doses of mecholyl as large as 3 mg. On the other hand, the prior intra-arterial administration of mecholyl may not only produce sufficient local vasodilatation to allow the subsequently administered epinephrine to reach the general circulation, but also may delay the local response of the latter drug, a phenomenon which suggests that epinephrine under such conditions remains in the local tissues and is potentially active for a relatively long period of time.

(7) Benzedrine sulfate when injected intra-arterially produces general effects but not especially marked local effects. In other words, this drug is not easily destroyed by the tissues and consequently may circulate for a considerable period of time. It is noteworthy that acetylcholine, mecholyl, and epinephrine cannot be administered by mouth with any degree of success, whereas benzedrine sulfate is effective when so administered. It is probable that the potentiality of a drug for oral administration may be tested by observing its effects when injected intra-arterially.

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THE CLINICAL SIGNIFICANCE OF A PERSISTENT DEPRESSION OF THE RS-T SEGMENT IN THE ELECTROCARDIOGRAM

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I. INTRODUCTION

IN THE last ten years, since the electrocardiogram ceased to be a method of analyzing disorders of the cardiac rhythm only and became an important aid in the diagnosis of other diseases of the heart, much stress has been laid on deviation of the RS-T segment from the isoelectric line. These deviations in acute coronary occlusion, as described by Pardee[1] and analyzed and classified by Parkinson and Bedford[2] and Barnes and Whitten,[3] are well known. Similar changes have been described in transient myocardial ischemia. Depression of the RS-T segment with or without inversion of the T-wave has been seen both in attacks of spontaneous angina pectoris and that provoked by exercise (Feil and Siegel,[4] Parkinson and Bedford,[5] Brow and Holman,[6] Goldhammer and Scherf,[7] Hausner and Scherf[8]). It has been shown that general anoxemia induced by breathing of an oxygen-poor mixture causes a depression of the RS-T segment not only in patients with an insufficient coronary circulation, but also in normal subjects (Rothschild and Kissin,[9] Katz and Hamburger[10]). Büchner[11] found similar changes in the electrocardiogram of rabbits after an acute massive hemorrhage and demonstrated small areas of necrosis in the heart muscle of these animals. Electrocardiographic changes of this type were found in man in anemia,[12] hypoglycemia,[13] carbon monoxide poisoning and in other conditions, the common feature being a state of malnutrition of the heart muscle. Among other causes of RS-T deviation are certain drugs, especially digitalis,[14] infections[15] (acute rheumatism, diphtheria), pericarditis,[16] and pulmonary embolism.[17]

There are, however, cases in which the deviation of the RS-T segment is permanent and progressive. Pardee[18] described this abnormality of the electrocardiogram and considers that the cause of it is unknown. He suggests that the contraction process may develop potential sooner after QRS because of the greater activity of the hypertrophied muscle. On the other hand, Weber and his associates[19] accept a depression of the RS-T segment with or without an inverted T-wave as the most characteristic sign of an inadequate blood supply

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to the heart muscle, which they call "coronary insufficiency." Their theory, based on the above cited experiments of Büchner, has found its way into most textbooks of electrocardiography written in the German language,[20] although it has been criticized lately by Schellong and his associates.[21]

In the routine electrocardiographic work in this department I noticed that a persistent depression of the RS-T segment is not an uncommon finding, and these investigations were carried out in order to see whether this abnormality is related to any special type of heart disease or syndrome.

II. METHODS OF INVESTIGATION

The investigations were carried out in the following way:

1. Electrocardiograms of 150 normal subjects between the ages of 15 and 40 years were used as controls.

2. Two thousand electrocardiographic curves taken in the routine work of the department in 1936 and 1937 were examined in order to discover the incidence of a permanent depression of the RS-T segment.

3. All cases of heart disease in which this abnormality occurred were analyzed, especially in regard to the relationship of the electrocardiogram to the clinical course of the disease.

The tracings were made either with the standard Cambridge string galvanometer or the Victor electrocardiograph. In about 40 per cent of the cases, in addition to standard leads, precordial leads were taken. The technique of the chest leads is described elsewhere[22]; the exploring electrode was placed at the apical, left pectoral, and right pectoral regions, and the indifferent electrode on the right arm or left leg.[23]

A permanent depression of the RS-T segment was diagnosed when two or more tracings taken within a month or more showed this change. In a few cases in which only one record was available, every possible factor influencing the electrocardiographic curve was considered before the cases were included in the series.

In measuring depression or elevation of the RS-T segment, care was taken to exclude apparent deviation due to exaggerated auricular T-waves,[24] to a prominent U-wave, or to respiratory effects upon the level of the base line. Technical faults, especially overshooting, were given due consideration. No cases of bundle branch block were included. Because of some difficulties in ascertaining the level of the RS-T segment, a few rules were followed: (1) The depression or elevation of the RS-T segment was measured from the base of the preceding P-R segment if the latter was horizontal. (2) When the P-R segment showed no distinct level, the RS-T segment was compared with the following T-P segment whenever possible. (3) Records in which the heart rate was over 110 were excluded because the RS-T segment was so shortened as to make it almost impossible to gauge its level.

From the clinical point of view particular stress was laid on presence or absence of angina pectoris, on the size of the heart as estimated radiologically, and on the presence or absence of heart failure.

III. RESULTS

A. NORMAL CONTROLS

The electrocardiograms of 150 healthy young people between 15 and 40 years of age were examined. It was found that both in the standard and in the chest leads the RS-T segment was almost invariably

isoelectric. In a very small proportion of cases there was a slight deviation of the segment above or below the isoelectric line in the standard leads, the maximum being 0.25 mm. In chest leads the deviation was more common but did not exceed 1 mm. It seems safe to conclude that the upper limit of normal variations is 0.5 mm. (0.05 mv.) in standard leads and 1.5 mm. (0.15 mv.) in chest leads.

B. ROUTINE ELECTROCARDIOGRAMS

Two thousand curves were examined, and 178 were found in which a persistent depression of the RS-T segment was present. In 56 of these the depression was due to digitalis, and these records were excluded from further study.

In the remaining 122 cases the following diseases were found:
Hypertensive heart disease in 69 cases,
Syphilitic aortic valvular disease in 19 cases,
Nonsyphilitis aortic valvular disease in 8 cases,
Coronary artery disease in 7 cases,
Rheumatic mitral valvular disease in 9 cases,
Cor pulmonale in 4 cases,
Congenital heart disease in 1 case,
Infective endocarditis in 1 case,
Myxedema in 2 cases,
Thyrotoxicosis in 2 cases.

These figures reveal that a depression of the RS-T segment may occur in all types of heart disease, the distribution of cases corresponding roughly to the frequency of the disease in the material examined.

Examination of the curves showed that permanent deviation of the RS-T segment may occur as a depression or as an elevation, but that the former was the more constant and the more striking. When elevation of the RS-T segment does occur, it is invariably as a reciprocal effect of the depressed RS-T segment in the opposed lead. It was found in 28 per cent of the present series and occurred only in association with left or right axis deviation. Thus in left axis deviation, when the RS-T segment is depressed in Lead I, it may be elevated in Lead III, the amplitude of the depression being usually greater than that of the elevation. The deviation always occurs in the opposite direction to that of the main ventricular complex. Elevation was never present in more than one lead and was never found in Lead II. It was not found in the absence of a more striking depression in the opposed lead.

Two types of RS-T depression can be distinguished: the common type shows a depression of the RS-T take-off, and the curve runs horizontally under the isopotential level into an upright, diphasic or inverted T_1. In other cases the RS-T depression simulates that pro-

duced by digitalis, in which the RS-T take-off is isoelectric or slightly depressed and the RS-T segment moves downwards in a straight line to an inverted or diphasic T-wave. This "sagging" RS-T depression occurred in 13 cases (11 per cent) in which digitalis treatment was excluded.

RS-T depression of the common type measured from 0.5 to 2 mm. in amplitude. It was found in one or two leads, but never in all three leads. It occurred particularly in cases of axis deviation in the lead in which the maximum QRS deflection was upwards, i.e., in Lead I in left axis deviation and in Lead III in right axis deviation. The facts are presented in Table I.

TABLE I

RELATIONSHIP OF DEPRESSION OF THE RS-T SEGMENT TO NORMAL OR ABNORMAL T-WAVES

TYPE OF ELECTROCARDIOGRAM	RS-T SEGMENT DEPRESSED IN ONE LEAD	RS-T SEGMENT DEPRESSED IN TWO LEADS	RS-T DEPRESSION AND ELEVATION IN THE OPPOSED LEAD
Normal axis with normal T-waves	6	9	–
Normal axis with abnormal (diphasic or inverted) T-waves	5	9	–
Left axis deviation with normal T-waves	11	11	10
Left axis deviation with abnormal T-waves	9	20	26
Right axis deviation with normal T-waves	1	1	–
Right axis deviation with abnormal T-waves	1	4	2
	33	54	38

In left axis deviation (87 cases) RS-T depression was found without abnormal T-waves in 32 cases, or 37 per cent. In the remainder depression of the RS-T segment occurred in association with isoelectric, diphasic or inverted T-waves. The depression tended to be more marked in Lead I than in Lead II. Many curves showed, in addition, an elevation of the RS-T segment in Lead III. In most of these cases left axis deviation was well marked, and the QRS complexes were of high voltage and were often widened to 0.1 sec., especially when T_1 or T_1 and T_2 were inverted. This type of electrocardiogram, which is similar to that of left bundle branch block, is well known in cases of marked left ventricular preponderance.

In cases of right axis deviation the opposite was found, i.e., the depression of the RS-T segment was present in Lead III or in Leads II and III, and elevation, if any, was present in Lead I.

In 15 cases (52 per cent) in which there was neither right nor left axis deviation, depression of the RS-T segment occurred with normal T-waves in Lead I or II, or in both, and in three cases, in Leads II and III. When present in two leads the depression was more

marked in Lead II than in Leads I or III. In other cases the RS-T changes were generally in accord with the changes in the T-waves.

In 49 cases (38 per cent) chest leads were studied in addition to standard leads. Both depression and elevation were noticed, the latter being more frequent. It was found that depression was most marked in the apical lead, whereas elevation always increased the more the exploring electrode was shifted to the right of the precordium. In comparing the occurrence of deviations in standard and in chest leads it was found that these changes were more common in standard leads, and only in very few cases were they present in chest leads exclusively. It seems that chest leads are not helpful in revealing permanent depressions of the RS-T segment.

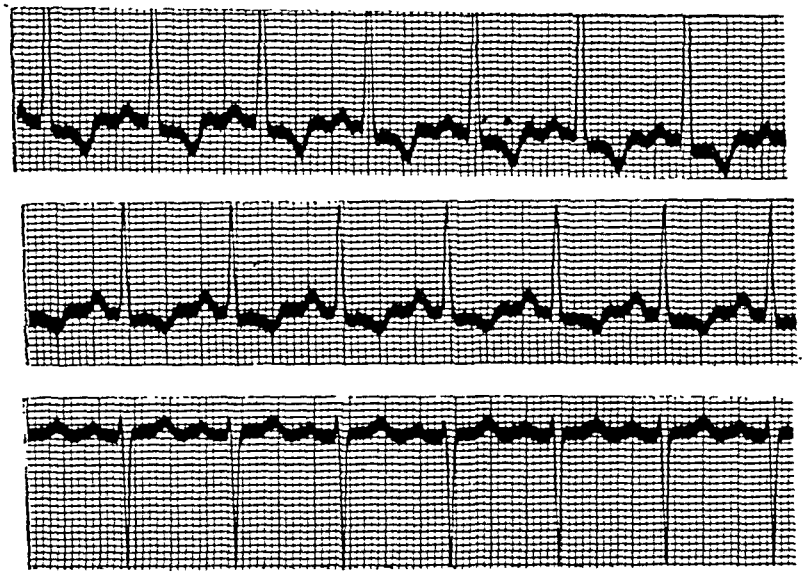

Fig. 1.—Left axis deviation with inversion of the T-wave in Leads I and II and depression of the RS-T segment in these leads. The RS-T segment in Lead III is slightly elevated. Clinically, a case of hypertensive heart disease with considerable enlargement of the left ventricle, proved by post-mortem examination.

C. CLINICAL INVESTIGATIONS

The data so far described were obtained from unselected electrocardiograms. They will now be considered in relation to the type of heart disease present.

1. *Hypertensive Heart Disease.*—Clinical, radiologic and electrocardiographic studies were made in 114 cases in which digitalis was not being given. These cases were divided into three groups, according to symptoms: A, No symptoms; B, slight to moderate effort dyspnea; C, left- or right-sided heart failure. In each group cases in which there was clinical evidence of coronary artery disease (angina pectoris or myocardial infarction) were considered separately. The results are presented in Table II, which reveals that depression of the RS-T

segment becomes more frequent with increase of signs and symptoms. The figures are 13 cases, or 45 per cent, with depression of the RS-T segment in Group A; 24 or, 52 per cent, in Group B; and 32, or 82 per cent, in Group C. The frequency of normal curves naturally declines in these groups: Group A, 52 per cent; B, 37 per cent; C, 7 per cent. A decrease in the incidence of curves in which the depression of the RS-T segment is the only abnormality can also be noted: Group A, 36 per cent; B, 25 per cent; and C, 10 per cent. It is therefore evident that the worse the state of the heart, the higher the incidence of abnormal electrocardiograms and the greater the degree of abnormality.

TABLE II

DEPRESSION OF THE RS-T SEGMENT IN THE THREE GROUPS OF CASES OF HYPERTENSIVE HEART DISEASE

TYPE OF ELECTROCARDIOGRAM	GROUP A				GROUP B				GROUP C			
	RS-T NORMAL		RS-T DEPRESSED		RS-T NORMAL		RS-T DEPRESSED		RS-T NORMAL		RS-T DEPRESSED	
	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA	NO ANGINA	WITH ANGINA
Normal axis with normal T-waves	2	—	3	1	15	1	—	1	1	—	1	—
Normal axis with abnormal T-waves	—	—	2	—	2	2	2	1	—	—	2	1
Left axis deviation with normal T-waves	13	—	2	1	3	—	9	1	2	—	4	2
Left axis deviation with abnormal T-waves	1	—	4	—	1	—	7	3	2	—	17	5
Total	16	—	11	2	21	3	18	6	5	—	24	8

Comparing the anginal and nonanginal groups it can be seen that there were 19 cases (16.5 per cent) of hypertensive heart disease with angina pectoris, in 16 (84 per cent) of which depression of the RS-T segment occurred, whereas in only 53 (56 per cent) of the hypertensive nonanginal cases was this depression present.

2. *Aortic Valvular Disease.*—This group was divided into syphilitic cases with angina pectoris, syphilitic cases without angina, and nonsyphilitic cases in which angina did not occur. In the rheumatic group cases of mitral stenosis were excluded. Table III shows this comparison. The ratio of normal to depressed RS-T segments in the syphilitic nonanginal group was 2:11; in the syphilitic group with angina pectoris, 4:7; and in the nonsyphilitic group, 1:9. Thus the incidence of curves with the depressed RS-T segment was greater in the nonanginal syphilitic group than in cases with angina and was greatest in the nonsyphilitic group. These findings are important and will be discussed later.

TABLE III

COMPARISON OF SYPHILITIC AND NONSYPHILITIC AORTIC VALVULAR DISEASE

TYPE OF ELECTROCARDIOGRAM	SYPHILITIC AORTIC VALVULAR DISEASE WITHOUT ANGINA		SYPHILITIC AORTIC VALVULAR DISEASE WITH ANGINA		NONSYPHILITIC AORTIC VALVULAR DISEASE	
	RS-T NORMAL	RS-T DEPRESSED	RS-T NORMAL	RS-T DEPRESSED	RS-T NORMAL	RS-T DEPRESSED
Normal axis with normal T-waves	—	1	1	—	—	2
Normal axis with abnormal T-waves	—	2	1	1	—	2
Left axis deviation with normal T-waves	2	—	1	3	1	5
Left axis deviation with abnormal T-waves	—	8	1	3	—	—
Total	2	11	4	7	1	9

3. *Coronary Artery Disease.*—Twenty-five patients with angina pectoris or a history of myocardial infarction were examined (Table IV).

TABLE IV

DEPRESSION OF THE RS-T SEGMENT IN CORONARY DISEASE

TYPE OF ELECTROCARDIOGRAM	ANGINA PECTORIS		CORONARY OCCLUSION	
	RS-T NORMAL	DEPR.	RS-T NORMAL	DEPR.
Normal axis with normal T-waves	5	1	3	–
Normal axis with abnormal T-waves	1	1	1	–
Left axis deviation with normal T-waves	1	2	1	–
Left axis deviation with abnormal T-waves	2	2	4	1
Total	9	6	9	1

In 18 cases the RS-T segment was normal, and in seven it was depressed. When the groups of cases with angina and of cases with healed myocardial infarcts are studied separately, it can be noted that in the first group the ratio of normal to depressed RS-T segment was 9:6, and in the latter 9:1. In the second group 10 patients were studied who had had typical attacks of coronary occlusion from four months to two years earlier; the electrocardiograms showed evidence of old myocardial infarction of the Q_1T_1 type in 6 cases and of the Q_3T_3 type in 4 cases. In this group depression of the RS-T segment was present in only one case, and it should be noted that this case was complicated by aortic stenosis with considerable enlargement of the left ventricle.

Many patients of this group showed some enlargement of the left ventricle due to some complication such as hypertension, but in 10 out of 15 cases with normal RS-T segments the size of the heart was normal, whereas in the group with RS-T depression only 2 hearts were of normal size.

It is clear that in angina pectoris a depression of the RS-T segment is not uncommon, but in healed myocardial infarction it is very rare.

Other types of heart disease were not analyzed separately because of the rarity of the associated RS-T depression in the material examined.

4. *Relationship of Enlargement of the Heart to RS-T Depression.*—The size of the heart, especially of the left and right ventricles, was gauged by radiologic examination (radioscopy and teleoradiogram). Cases were classified and put into five divisions. Estimation of the size of the heart is not very easy and is subject to many errors, but all the patients were examined by the same observer (Dr. P. H. Wood). The results are shown in Table V.

TABLE V

RELATIONSHIP OF RS-T DEPRESSION TO ENLARGEMENT OF THE LEFT AND RIGHT VENTRICLES

	RS-T DEPRESSED	RS-T NORMAL
Left ventricular group:		
No enlargement	4 (31%)	9 (69%)
Slight enlargement	19 (43%)	25 (51%)
Moderate enlargement	21 (52%)	20 (48%)
Considerable enlargement	47 (90%)	5 (10%)
Gross enlargement	9 (100%)	-
Right ventricular group:		
Slight enlargement	3	5
Moderate enlargement	1	-
Gross enlargement	4	-

It is seen that the incidence of RS-T depression in Lead I increases as the size of the left ventricle increases and that the depression of that segment in Lead III runs parallel to the degree of right ventricular enlargement. Depression of the RS-T segment in Lead II was found to depend more upon deviation of the electrical axis than upon the size of the ventricles; it usually occurred with the lesser degrees of axis deviation.

5. *Post-Mortem Examinations.*—An autopsy was performed in 21 cases—11 cases of hypertensive heart disease, 2 cases of syphilitic aortic incompetence, 5 cases of primary coronary artery disease, 2 cases of mitral stenosis, and 1 case of cor pulmonale. The size of the ventricle was estimated, and the coronary arteries were carefully examined. Some of the cases will be included in a series shortly to be reported by Harrison and Wood, and in these the coronary arteries were examined by injections of a radiopaque substance.

Of the 11 hearts from patients who had had hypertension, 7 exhibited the unduly wide coronary arteries which are common in this disease (Harrison and Wood). Of these, 6 had gross left ventricular enlargement and the electrocardiograms of 5 had shown left axis deviation with depression of the RS-T segment in Lead I, or in Leads I and II with or without elevation of that segment in Lead III. In

other cases of hypertension the coronary arteries showed severe atheromatous changes causing irregularities of the outline with narrowing of the lumen. In these cases hypertrophy of the left ventricle was also gross, and the electrocardiogram had shown depression of the RS-T segment in Lead I in all of them.

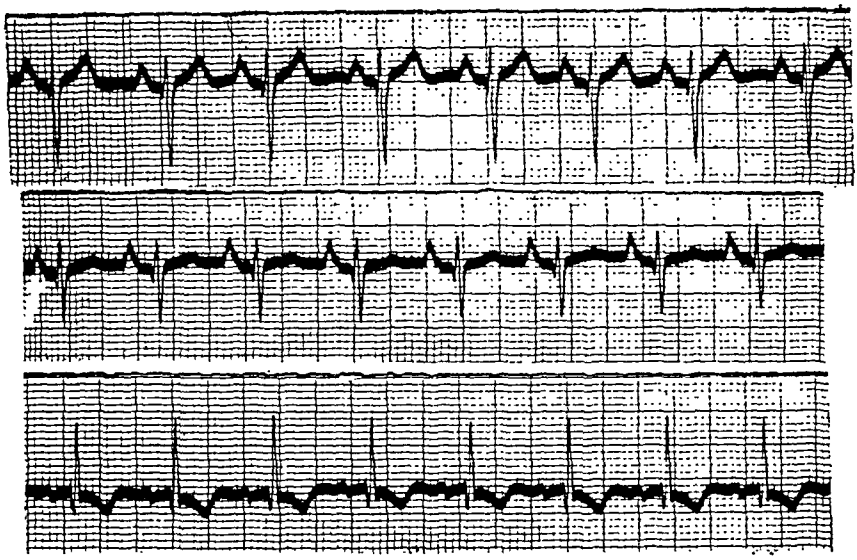

Fig. 2.—Right axis deviation with inversion of the T-wave and depression of the RS-T segment in Lead III and slight elevation of that segment in Lead I. Clinically, a case of chronic cor pulmonale with considerable enlargement of the right ventricle (post-mortem proof). Age of patient, 29 years.

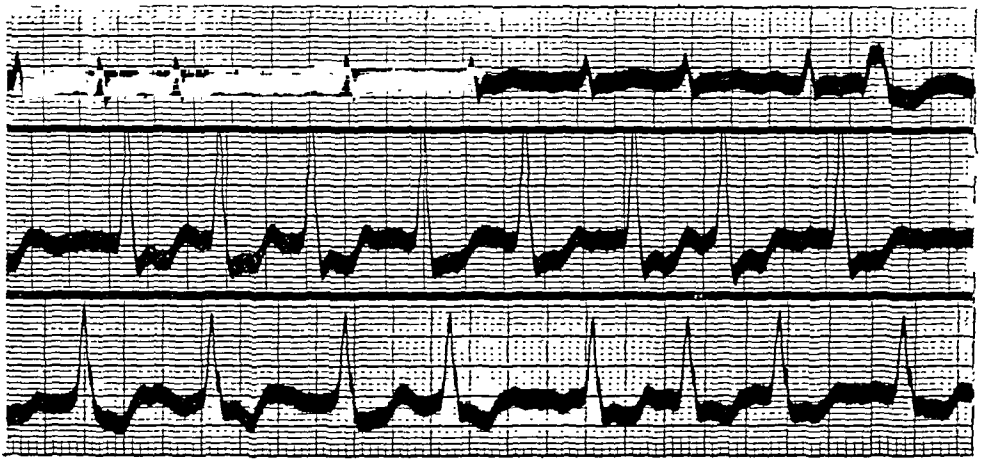

Fig. 3.—Normal electrical axis. Auricular fibrillation. Marked depression of the RS-T segment in Leads II and III. Clinically, a case of malignant hypertension with uremia, chronic bronchitis, and emphysema. Post-mortem examination showed considerable hypertrophy of the right ventricle (due to pulmonary disease) and only slight hypertrophy of the left ventricle.

In the 5 cases of occlusive coronary atheroma the left ventricle showed only slight if any hypertrophy. In 4 cases of this group there had been no abnormality of the RS-T segment in the electrocardiogram; in one a slight depression of the RS-T segment occurred in Lead I.

In both cases of syphilitic aortic incompetence the left ventricle was hypertrophied and the coronary ostia were markedly stenosed. In one case the electrocardiogram had been normal, and in the other there was a depression of the RS-T segment in Leads I and II.

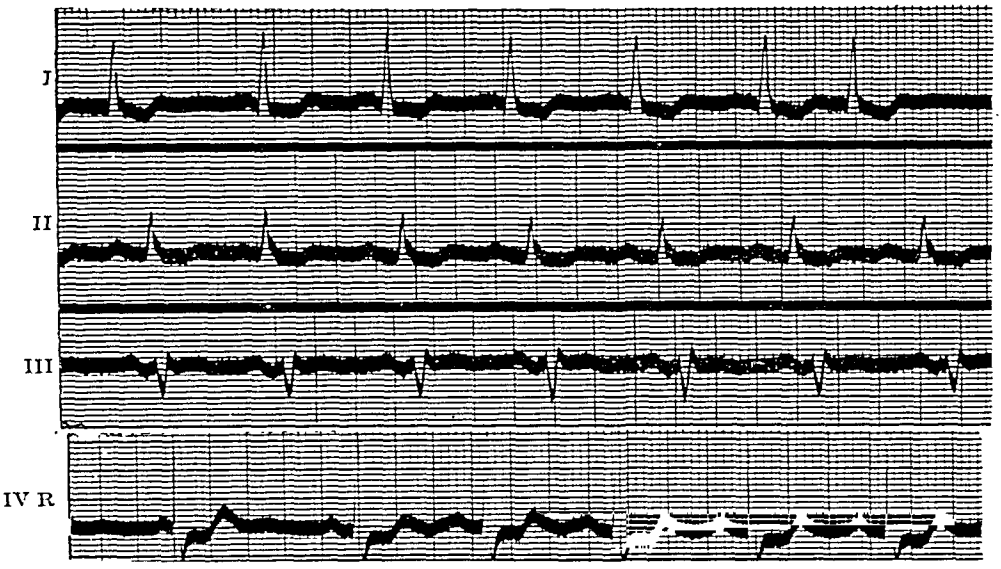

Fig. 4.—Left axis deviation with depression of the RS-T segment in Leads I and II and very marked depression of that segment in Lead IV R. Clinically, a case of hypertensive heart disease with moderate enlargement of the left ventricle (demonstrated radiologically).

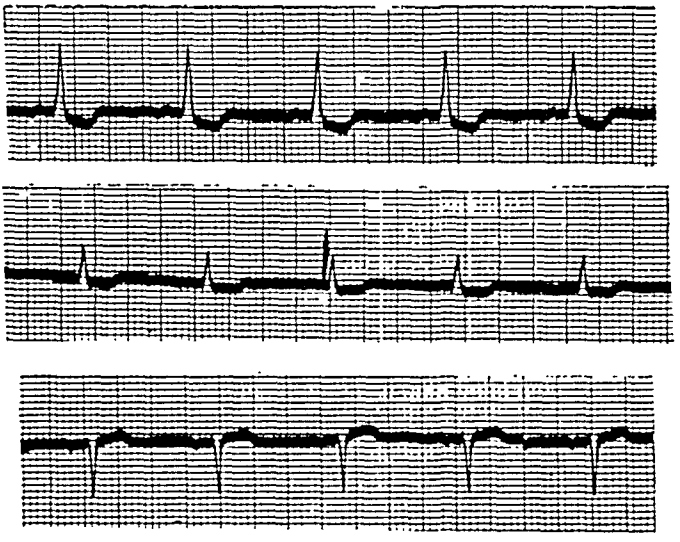

Fig. 5.—Left axis deviation with digitalis-like depression of the RS-T segment in Leads I and III and reciprocal elevation of that segment in Lead III. Clinically, a case of hypertensive heart disease with heart failure. No angina pectoris.

In the 3 cases of marked right ventricular hypertrophy the coronary arteries were normal (the oldest patient was 33 years old); the electrocardiogram had shown right axis deviation with a depression of the RS-T segment in Leads II and III.

IV. COMMENT

In discussing these results three questions are to be answered:

1. Is depression of the RS-T segment a definitely pathologic sign?

2. Does it occur as a specific change in one type of cardiac lesion only?

3. Are the deviations of the RS-T segment valuable as an aid in diagnosis?

1. The results of this study, which agree with those of other observers, show that deviation of the RS-T segment does not occur under normal circumstances in health. Temporary changes are not necessarily significant. They occur after violent exercise,[21b] in general anoxemia,[9] carbon monoxide poisoning,[19a] and as an effect of certain drugs,[14] but permanent changes do not occur unless disease of the heart is present.

2. The second question is more difficult to answer and must be considered more fully. From an etiologic point of view it has been shown that depression of the RS-T segment occurs in all types of heart disease. More important, however, is the anatomic site of the lesion. As no case of acute cardiac disease was included in this series, there are only two factors which have to be considered, namely, cardiac enlargement and occlusive coronary atheroma. Cases of predominantly left-sided heart disease were divided into three groups: enlargement without coronary artery disease, enlargement with coronary artery disease, and coronary artery disease with little or no enlargement. It is true that in most cases this division was made on the basis of clinical and radiologic examinations, without post-mortem control, and the clinical criteria for the diagnosis of coronary artery disease (angina, old cardiac infarction) are not very reliable, as there may be definite coronary disease without detectable signs and symptoms. The resulting figures, however, when examined critically, are of value. The incidence of RS-T depression in the first two groups does not differ materially. In the third group, in which coronary artery disease was established beyond doubt, the incidence of changes in the RS-T segment was found to be much lower than in the former groups. This was confirmed conclusively by the group of cases in which post-mortem examination was performed. On the other hand, it is seen that the incidence of deviation of the RS-T segment increases with the severity of the lesion and with the degree of the enlargement of the left (or right) ventricle. This relationship between left (or right) ventricular enlargement and the described changes in the electrocardiogram seems to be the most important result of these investigations. No relationship could be found between permanent depression of the RS-T segment and occlusive coronary atheroma. On the contrary, RS-T depression was less common

in angina pectoris and did not occur at all in uncomplicated cases of myocardial infarction in which coronary disease is certainly most advanced and severe.

As has been mentioned, certain authors believe that RS-T depression is a specific change in coronary insufficiency, but they place cardiac enlargement also in that category. It is a matter of opinion whether this is justified. It has been argued by T. R. Harrison[25] that the ultimate cause of heart failure in cardiac enlargement is probably anoxemia of the muscle, caused by the fact that blood cannot be delivered in sufficient amounts to the grossly hypertrophied organ. For theoretical reasons, perhaps, cardiac enlargement can be grouped with coronary insufficiency, but from the practical point of view I think that this cannot be accepted. Clinical and anatomic facts are against it. Uncomplicated hypertensive heart disease, which progresses almost invariably into left- and right-sided heart failure, is a typical clinical entity with clear-cut signs, symptoms, course, and prognosis and differs materially from ischemic heart disease. The same difference in symptoms and prognosis is seen between cases of syphilitic and rheumatic aortic valvular disease, although the anatomic findings, apart from those in the coronary arteries, are identical. It has been mentioned that Harrison and Wood found in uncomplicated cases of hypertensive heart disease enlarged coronary arteries with increased vascularity of the hypertrophied muscle, whereas in other cases the arteries were narrow and irregular and the vascularity poor.

These two entities, therefore, are entirely different diseases and cannot be considered together in a common group.

The great progress in cardiology is to some extent due to modern classification of heart disease, mostly by American authors (*Criteria for the Classification and Diagnosis of Heart Disease*, ed. 3, 1931) and to use the term "coronary insufficiency" to include both groups would be a retrograde step.

The second question, therefore, can be answered by saying that depression of the RS-T segment is very closely related to enlargement of one of the ventricles, although it is not a specific sign of this abnormality. It occurs in left ventricular enlargement in Lead I and in right ventricular enlargement in Lead III.

3. It has been shown that depression of the RS-T segment occurs in all types of heart disease. In advanced stages it is more marked and is as a rule accompanied by changes in the T-waves. In considering the relationship of the changes in the RS-T segment to the changes in the T-waves, it is to be noted that they both occur in similar conditions. Any factor which causes temporary RS-T deviation (angina pectoris, coronary occlusion, digitalis, anoxemia, etc.) affects also the T-waves, if not simultaneously, then at a later stage. It is highly probable that persistent changes in these two parts of

the electrocardiographic curve are also of the same nature, caused by the same process. Therefore, if both changes are found in the same electrocardiogram, the diagnostic value of the deviation of the RS-T segment is limited because changes in the T-waves are more conspicuous and more readily recognized. There are, however, cases in which deviation of the RS-T segment can be of some help in the diagnosis. It has been shown that in electrocardiograms with axis deviation there are often a depression and an elevation of the RS-T segment in the two opposed leads, i.e., deviation in the opposite direction to the main QRS complex. This occurs most frequently in cases in which there is already electrocardiographic evidence of considerable enlargement of one of the ventricles, i.e., marked axis deviation with high voltage and slight prolongation (up to 0.1 sec.) of the QRS complex and T-waves in the opposite direction to the main ventricular complex. But in a number of cases changes in the RS-T segment occur earlier than QRS and T changes. It has been stated that depression of the RS-T segment in one lead and elevation in the opposed lead occur only when there is an enlargement of one ventricle, and this may be of value. Left axis deviation can be caused by several factors and does not necessarily mean left ventricular enlargement, but left axis deviation with depressed RS-T_1 and elevated RS-T_3 means moderate to considerable enlargement of the left ventricle. It has the same meaning as if T_1 were inverted and T_3 upright. The same statement applies to right axis deviation, i.e., right axis deviation with depressed RS-T_3 and elevated RS-T_1 means predominant enlargement of the right ventricle.

There is another group of cases in which RS-T deviation can be of diagnostic value—cases in which more than one factor is influencing the electrocardiographic curve. It happens not infrequently that there is no abnormal axis deviation when one would expect it to be present; this may be the resultant of two opposing factors, such as mitral and aortic valvular disease, hypertension and a low position of the diaphragm, etc. In some of these cases the RS-T segment is depressed in two leads, and this may be of help; a normal position of the electrical axis with depression of the RS-T segment in Leads I and II means that the left side of the heart is mainly affected, whereas a depression of that segment in Leads II and III means that the right side of the heart is the more involved.

I hope to be able to show in a subsequent paper that this statement applies not only when there is a persistent depression of the RS-T segment, but also when this depression is caused by digitalis. This widens the diagnostic value of this observation, as distortion of the electrocardiogram caused by digitalis is very common, and in many cases in when there is no axis deviation and the drug causes a conspicuous depression of the RS-T segment, the lead in which this effect occurs may indicate the chamber which is most enlarged.

Last, there is a group of cases in which the depression of the RS-T segment is the only abnormality of the electrocardiogram. It has been said that such a depression is definitely abnormal and therefore that electrocardiograms in which it occurs are to be considered as indicating disease. Although most often associated with cardiac enlargement, depression of the RS-T segment has, in common with an abnormal T-wave, a manifold meaning. Generally it can be considered as a forerunner of a T-wave inversion. In the material examined it was found that in early cardiac disease depression of the RS-T segment occurs as the only abnormality of the electrocardiogram, but in more severe cases it is likely to be combined with abnormal T-waves. This seems to justify the statement that a depression of the RS-T segment is an early abnormal sign having the same significance as a pathologic T-wave (with the exception of old cardiac infarction) and that, when it appears, changes in the T-waves are to be expected.

As stated above, the diagnostic value of the chest leads in detecting early changes of the RS-T segment in the electrocardiogram is limited.

V. CONCLUSIONS AND SUMMARY

1. A persistent depression of the RS-T segment in the electrocardiogram is an abnormality of importance.

2. It is usually most marked in the lead in which the main ventricular complex shows the maximum upward deflection. In some cases there is an elevation of the RS-T segment in the opposed lead, i.e., when there is depression in Lead I, there may be elevation in Lead III, and vice versa. The elevation, however, is a later and less important change.

3. Depression of the RS-T segment is most often associated with enlargement of the left or right ventricle and usually occurs as a forerunner of T-wave inversion. It occurs in left ventricular enlargement in Lead I, or in Leads I and II; in right ventricular enlargement it is found in Lead III, or in Leads II and III. Usually it is found in conjunction with right or left axis deviation, but it has the same significance in curves in which there is no abnormal deviation of the axis.

4. The statement of many German authors that the depression of the RS-T segment is a specific sign of coronary insufficiency is not confirmed.

I wish to express my thanks to Prof. F. R. Fraser and to Dr. P. H. Wood for their criticism and help in preparation of this article. I am indebted to Sir Frederick Menzies, Chief Medical Officer of the London County Council, for his permission to utilize the material of the hospital.

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FURTHER OBSERVATIONS ON APICAL SYSTOLIC MURMURS IN CHILDREN*

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IN 1932 we published a paper[1] in which we reported the results of our study of apical systolic murmurs in 100 children whom we had followed for six or more years. At that time we observed that (1) 30 per cent of the children developed severe organic heart disease (mitral stenosis, aortic insufficiency, or both); (2) 50 per cent of those who gave a history of rheumatic fever or chorea developed serious organic heart disease; (3) among those who had physical signs of enlargement of the heart at the first examination, 37 per cent developed serious organic heart disease; (4) of those whose cardiac enlargement was demonstrated by means of the orthodiagram, 40 per cent developed serious cardiac disease; (5) only 9 per cent of those whose hearts were entirely normal fluoroscopically developed further evidences of cardiac disease; (6) in only 8 per cent of the patients did the murmur disappear completely; (7) only one of the seven patients who were five years of age or under developed organic heart disease, and this patient had an attack of chorea when she was eight years old, following which she developed mitral stenosis; (8) the electrocardiogram seemed to be of no value in estimating the prognosis.

As considerable time has elapsed since the original study was made, we thought it advisable to re-examine as many of the patients as possible in order to get a still better idea of the significance of apical systolic murmurs in children. In the present report only patients who have been followed for ten years, or more, are included. The series is not very large because it is difficult to follow young people in a clinic for more than ten years; they grow up and leave town, marry, or become prosperous and are lost sight of. However, since those who are not doing well are usually the ones who keep in touch with the clinic, our statistics tend to paint a picture which is somewhat too gloomy.

We have been able to follow 33 (15 males and 18 females) of the original 100 patients for ten years, or more.† The period of observation ranged from ten to sixteen years, averaging more than twelve years. Seven of the patients had mitral stenosis alone, one had aortic

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†Since 1932, one death has been reported to us. The patient was a girl whom we had followed for seven years. She died at the age of 15 of subacute bacterial endocarditis. This was the second fatality known to have been caused by subacute bacterial endocarditis in the original group of 100 patients.

insufficiency alone, and one had both mitral stenosis and aortic insufficiency. This makes a total of nine patients (27 per cent) who developed serious valvular heart disease. At the time of our first study this proportion was about the same (30 per cent). In four cases (12 per cent) the murmur had disappeared entirely; this occurred in 8 per cent of the original series. Twenty of the 33 patients (61 per cent) still had systolic murmurs, and nothing more; this is exactly the same proportion as in the group of 100. No new cases of mitral stenosis or aortic insufficiency had developed since the previous study. Therefore, our original statement that mitral stenosis was first diagnosed between one and nine years (average 4.7 years) after the discovery of a systolic murmur is still valid. Aortic insufficiency occurred somewhat earlier; the diagnosis was made, on the average, within three years after discovery of the systolic murmur.

In our previous study we had tried to ascertain whether the presence of fever had any prognostic significance, and at that time we considered an oral temperature of 99° F., or above, on at least two successive visits, as evidence of fever. However, we found that most of our patients had such temperatures at one time or another, and concluded that this was of no prognostic significance. In our present series it was found that, according to this standard, 75 per cent of the patients had fever. When we made our criteria of fever more strict, and considered only temperatures of 99.6° F., or above, on three successive visits, as significant, we were still unable to draw any conclusions, for only one patient's temperature exceeded this limit. However, it must be remembered that we were dealing only with ambulatory patients who might not have been brought to the clinic at times when their temperatures were elevated. For the purpose of ascertaining accurately the prognostic significance of fever it will probably be necessary to have the temperatures taken daily at home. Nevertheless, our observations indicate that a slight elevation of temperature (between 99 and 100° F.) does not appear to have any prognostic significance.

Unfortunately, the blood pressures of children and young adults were not measured routinely in our clinic, so that we have blood pressure data in only eight cases. Four of these patients showed a tendency to hypertension at an early age (a patient with mitral stenosis had a blood pressure of 140/100 at the age of 20 years, and three patients with only systolic murmurs had pressures of 160/84, 140/80, and 140/90, at the ages of 21, 20, and 27 years, respectively). The question of the development of hypertension in patients who had systolic murmurs in childhood might be worth further investigation.

CONCLUSIONS

1. Of 33 children with apical systolic murmurs who were followed for more than ten years, 27 per cent developed serious valvular heart

disease (chiefly mitral stenosis), 61 per cent still had systolic murmurs and nothing more, and 12 per cent lost their murmurs entirely.

2. Those who developed mitral stenosis did so between one and nine years (usually between four and six years) after the discovery of the original murmur.

3. Slight elevation of temperature in children with apical systolic murmurs is of no significance as a prognostic sign.

4. There is a possibility that children with apical systolic murmurs have an abnormal tendency to develop early hypertension.

5. Conclusions drawn after following 100 children with systolic murmurs for six years[1] were unshaken by following 33 of the same children for an additional period of four years, or more.

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PANCREATIC NECROSIS ASSOCIATED WITH AURICULAR FIBRILLATION AND FLUTTER

Report of a Case Simulating Coronary Thrombosis (Autopsy Findings)*

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PANCREATIC necrosis associated with auricular fibrillation has been found but once in an exhaustive survey of the literature.[1] In that instance Drummond observed a rapid, complete arrhythmia in a case of pancreatitis which disappeared after the acute attack had subsided.

Nothnagel,[2] in 1876, enumerated the various extracardiac causes of arrhythmia and dwelt particularly upon the comparatively small group of individuals who had arrhythmias and apparently normal hearts. Orgain, Wolff, and White[3] have recently (1936) reviewed this entire subject, classifying the various extracardiac causes of auricular fibrillation and auricular flutter as found in the literature.

The rarity of pancreatic necrosis causing auricular fibrillation, the cardiac nature of many of the patient's complaints with confirmatory physical findings and laboratory analyses, and the complete post-mortem study have prompted the following report.

CASE REPORT

J. P., No. D1627-37, a 53-year-old bartender of Czechoslovakian birth, was first seen by one of us (E.L.D.) March 16, 1937, four hours after the onset of sharp upper abdominal pain, of a constant burning character, following indiscretions both in eating and drinking. Associated symptoms included gaseous eructations, nausea, orthopnea, and substernal oppression. The patient had had somewhat similar, although very much milder, experiences two years, one year, and five days before, respectively. Since the first of these attacks associated with abdominal pain radiating to the right shoulder, which confined him to bed for only one day, he had suffered from dyspnea on slight exertion but had shown no other signs of congestive heart failure.

The patient's past history included measles, whooping cough, and bronchopneumonia in childhood, typhus fever at the age of 19 years, and chronic bronchitis for the past ten to fifteen years; he attributed the latter to the fact that he was accustomed to smoke forty to sixty cigarettes daily. He drank heavily of both coffee and beer.

Physical examination revealed an orthopneic, cyanotic, cold, clammy, obese, extremely restless individual, seated on the edge of the bed, apparently in severe pain and holding his upper abdomen firmly. The rectal temperature was 99° F. His face was ashen, his lips blue, and his entire body bathed in a cold perspiration. Examination of the mouth revealed a coated tongue, a foul breath, and a number of carious teeth. There were no abnormal pulsations in the neck, and no engorgement of the cervical veins was noted. The lungs were negative except for occasional coarse

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TABLE I
LABORATORY FINDINGS

	3/16	3/17	3/18	3/22	4/2	4/3	4/7	4/8	4/10	4/16	4/19	4/23
Blood Count:												
Hb. (%)	106				80							80
R. B. C.	5.09				4.31							4.15
W. B. C.	19.9				22.2	21.8		14.5		13.2		11.3
Neutrophiles	83				87	81		72		88		77
(Mature)	(71)				(62)	(51)		(37)		(48)		(34)
(Immature)	(12)				(25)	(31)		(35)		(40)		(43)
Lymphocytes	17				10	4		25		12		18
Eosinophiles						2						
Monocytes					3	13		3				3
Myelocytes												2
Anisocytosis						Marked						
Polychromatosis						Moderate				Slight		
Macrocytosis						Moderate						
Microcytosis						Moderate						
Achromia										Slight		
Icteric Index				20.2					10.6			
Sedimentation Rate:												
mm. in hr.	2		17			20						
cell vol. %	68		52			52						
Blood Chemistry (mg. %):												
N.P.N.		45.1									27.9	
Urea				19.0					13.5			
Creatinine				1.76					1.36			
Protein (Total mg. %)					8.59							
Chloride											396	
CO_2 combining power (vol. %)											68	
Feces:												
Neutral Fat					Small amount					Very slight amount		
Fatty Acid					Many crystals					Occasional crystal		
Soaps					None					None		
Urinary Diastase							32		20		11	

râles heard over both lower lobes posteriorly. The apex beat of the heart was located in the fifth interspace, one inch to the left of the midclavicular line. There were no thrills. The auricles were fibrillating and the ventricular rate was 120 a minute, but there was no pulse deficit. The intensity of the aortic second sound was normal. No murmurs were heard. The blood pressure was 160/90. The abdomen was markedly obese and diffusely tender, but actual muscular spasticity was absent. The liver edge was palpable three fingerbreadths below the costal margin. The extremities showed no edema.

On admission to the hospital six hours later, after ¾ gr. of morphine sulfate in divided doses had failed to relieve his pain, the patient's status was little changed save that the blood pressure had fallen to 120/80, his rectal temperature had risen to 102° F., and his abdominal tenderness seemed more localized in the right upper quadrant.

Laboratory procedures with the exception of blood and urine sugar determinations are summarized in Table I. The latter are recorded in connection with dietary changes and insulin administration in Table II. The urine on the day of admission

TABLE II

SPECIAL RECORD: CASE NO. D1627-37

DATE	DIET TYPE	DIET CALORIES	INSULIN UNITS	URINE ACETONE	URINE SUGAR BENEDICT'S QUAL. SOL.	URINE DIACETIC ACID	BLOOD SUGAR (MG. %)	GLUCOSE INTRAVENOUSLY AMOUNT C.C.	GLUCOSE INTRAVENOUSLY CONCENTRATION %
3/16	Karell	800	0		Trace			50	25
								100	50
3/17	Karell		0		Trace		206.4	50	50
3/19	Carbohydrate 100	800	0		Trace				
3/22	Protein 60		0				375		
3/23	Fat 26		15-0-10		Trace				
3/24			15-0-10	Absent	Green	Absent			
3/25			15-0-10	Absent	Green	Absent	200		
3/27	Light		0				248		
3/28			0	Absent	Green	Absent			
3/29			0	Absent	Green	Absent			
3/30			0	Absent	Blue	Absent			
3/31			15-0-10	Absent	Blue	Absent		200	10
4/1			15-0-10						
4/2	Buttermilk		15-0-10				210.6	50	50
4/3			15-0-10		Blue			500	10
4/5			15-0-10					500	10
4/6			15-0-10					500	10
4/7			15-0-10					500	10
4/8	Light, variable		15-0-10		Blue			500	10
4/9	Negligible		15-0-10					500	10
4/10			15-0-10				157.4	500	10
4/11			15-0-10					1000	10
4/12			15-0-10		Blue			1000	10
4/13			15-0-10					1000	10
4/14			15-0-10					1000	10
4/15			15-0-10					1000	10
4/16			15-0-10		Yellow			1000	10
4/17			15-0-10					1000	10
4/19							193.6		

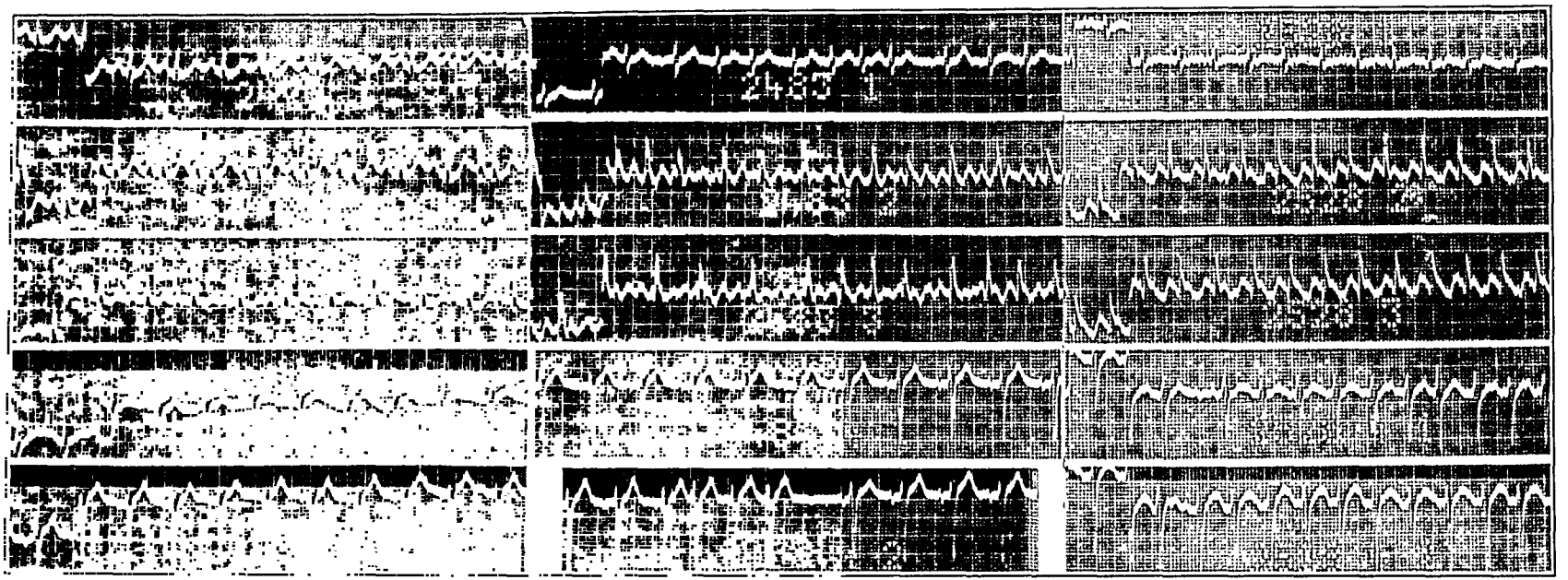

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—On admission, March 16, 1937, pulse rate 120, slowing of R, II, and thickening of R, IV-1,* are suggestive of some difficulty in spread of excitation wave through the ventricles, but there is no evidence of any frank intraventricular conduction defect as QRS time is not prolonged.

Fig. 2.—On March 18, 1937, Leads I, II, and III show impure flutter with rate of 390. Auriculoventricular block constantly varies, producing completely irregular ventricular beats. Average ventricular rate is 130 to 150. The ventricular complexes show some slurring and notching; there is no axis deviation. Lead IV-1 shows the normal sinus mechanism, rate 110, no conduction defects. Lead IV-2 shows two periods of irregularity, one due apparently to an auricular premature contraction and the other probably due to fibrillation. Conclusion: Impure flutter and fibrillation of paroxysmal type with rapid ventricular rate.

Fig. 3.—On April 3, 1937, the auricular oscillations were large and fairly regular and represented impure flutter rather than fibrillation; average ventricular rate, 160

*In Leads IV-1 and IV-2 the left electrodes are placed anteriorly.

showed a trace of albumin and of sugar and a few granular and hyaline casts, a few leucocytes, and several erythrocytes per high power field. The hemoglobin content was 106 per cent; the erythrocytes numbered 5,909,000, and leucocytes 19,900 per c.mm.; 71 per cent of the latter were mature polymorphonuclear cells, 12 per cent immature polymorphonuclear forms, and 17 per cent lymphocytes. Subsequent blood counts (Table I) showed a persistent leucocytosis of varying degree with the percentage of immature polymorphonuclear neutrophiles steadily rising until April 23, 1937, three days before death. The sedimentation rates ranged from 2 mm. in one hour on admission to 20 mm. in one hour during the third week of illness. Blood sugar determinations routinely yielded a high value, but showed a normal type of response to insulin therapy, as did also the urine sugar (Table II). With the exception of nonprotein nitrogen, which was slightly elevated on admission and subsequently returned to normal, all other blood chemical analyses were within usual limits (Table I). Serial electrocardiograms taken on March 16, March 18, and April 3, 1937 (Figs. 1, 2, and 3) showed varying degrees of auricular flutter of an impure type, slurring of the R-waves, and occasional extrasystoles. These changes were taken to indicate posterior myocardial infarction.

Clinically, the early course of the patient in the hospital definitely suggested that he had had coronary thrombosis. However, upper abdominal pain, burning, moderate fever, and diffuse tenderness persisted. Even small amounts of fluid food produced nausea and vomiting and, with the exception of milk, seemed to intensify the burning. Despite the diffuse abdominal tenderness there was very little rigidity, but towards the end of the second week of his illness, distention became marked and a small amount of free fluid could be detected in the flanks. Simultaneously, slight edema of the ankles and coarse râles at the bases of both lungs were noted. Moreover, cardiac irregularity, low blood pressure (110/80), and the electrocardiogram seemed to confirm the presence of coronary occlusion. In conjunction with the abdominal symptoms an intractable, profuse, very watery, offensive diarrhea supervened. Stool examination (Table I) indicated an increasing inability to digest fats. Urinary diastase was within normal limits on three occasions (32, 20, and 11 units, respectively). The patient grew worse progressively, with marked intensification of all abdominal phenomena and an exacerbation of fever during the four days preceding death on April 26, 1937.

*Autopsy** findings in the heart and pancreas may be summarized as follows:

The pancreas was found to be diffusely converted into a soft, dirty, grayish-brown, chalky mass resembling a sequestrum. Where the pancreas touched the duodenum a perforation, about 1 cm. in diameter, was found in the mesial wall of the duodenum. The tissues in this region were soft and gangrenous. This cavity communicated with the greater peritoneal sac through a perforation in the posterior peritoneum behind the duodenum. A similar perforation was seen in the wall of the colon which formed one side of this cavity.

Microscopically, the pancreas showed complete autolytic necrosis. The surrounding connective and fat tissue showed hyperemia, edema, and cellular infiltration. In other sections, coagulative and ischemic necrosis was present together with considerable precipitated blood pigment.

The heart weighed 450 gm. There was a moderate amount of free, contracting, "chicken-fat" clot in the right ventricle and auricle. The cardiac muscle was soft and flabby, pale red in color, and uniform in appearance throughout. A moderate amount of fat tissue was present beneath the epicardium. Both coronary arteries were patent throughout and on section presented smooth, intact intimae. The left

*Performed by Drs. W. E. Youland and G. Nagamatsu.

coronary artery presented a few miliary, flat, whitish plaques. Several small atheromatous plaques were seen in the ventricular endocardium near the aortic valve.

Serial microscopic sections taken from the interventricular septum showed an hypertrophy of the muscle fibers throughout. Multiple sections from each ventricle, including the coronary vessels, valvular cusps, and myocardium, showed a uniform degree of muscular hypertrophy, together with little if any myocardial fibrosis. One coronary vessel presented at its base slight to moderate fibrotic thickening of the intima and subintima, without calcific or obliterative changes.

The anatomicopathological diagnoses included: chronic obesity with myocardial hypertrophy; complete coagulative necrosis of pancreas with sequestration and massive fat necrosis of omentum, mesentery, and peritoneum (apparently cause of death); massive phlegmonous and gangrenous inflammation of retroperitoneum and lesser omental cavity communicating with the greater peritoneal cavity; gangrenous perforation of duodenum and colon; generalized serofibrinous peritonitis; cholelithiasis.

DISCUSSION

In retrospect, it is not difficult to trace the course of this acute gangrenous pancreatitis from its predisposing causes—obesity, alcoholism, and gallstones—through a series of attacks of acute indigestion closely following heavy eating and drinking, to a conclusion in the severe episode that constituted the patient's last illness. Careful analysis shows that the important features of acute pancreatic disease, as summarized by Deaver[4] and, more recently, by de Takats,[5] could be demonstrated in this patient. Nevertheless, certain aspects of the case warrant particular comment:

1. *The Cardiac Phenomena.*—A diagnosis of coronary occlusion was made clinically in view of the orthopnea, substernal as well as epigastric distress, the cardiac irregularities (which had never been present before), and the configuration of the electrocardiographic tracings. Indeed, in the first few days of his illness these phenomena, in conjunction with the nausea and vomiting, cyanosis, moderate rise in temperature, glycosuria, hyperglycemia, and leucocytosis, cast doubt upon the possibility of any other disease. Autopsy revealed the incorrectness of such a conclusion; all of the symptoms must have resulted from the intra-abdominal condition.

Among the intra-abdominal causes of functional cardiac disturbances, diseases of the gall bladder and biliary tract have long been conceded a first place. Biliary colic and its associated digestive disturbances may produce cardiac murmurs, tachycardia, bradycardia, arrhythmia, cardiac pain, and dyspnea.[6-17] Typical cardiac angina with radiation of pain to the left arm has been observed in hepatic[13, 18] and gastrointestinal disease.[8, 17-22]

Almost any and all of the inflammatory states, particularly those, such as ruptured peptic ulcer, which are associated with shock, have been noted to produce cardiac disturbances reflexly.[23] In the present

instance pancreatic necrosis, multiple intestinal perforations, and widespread peritonitis were all present. However, inasmuch as the cardiac dysfunction appeared early it seems logical to attribute it primarily to the pancreatic disease. Auricular fibrillation occurring in a normal heart as a complication of proved acute pancreatitis, as aforesaid, has been reported in the literature but once.[1] The present case is the first in which autopsy established with certainty the structural normality of the heart. This point seems to be of considerable importance, as it is known that subdiaphragmatic lesions not infrequently initiate cardiac symptoms when the heart is already damaged.[24-26] For instance, cholecystitis and arteriosclerotic heart disease exist in the same age group, but clinical evidence of the cardiac changes may be absent until an acute exacerbation of the gall bladder condition occurs.[26, 27] Moreover, in such a situation the removal of the gall bladder may relieve the cardiac symptoms, as, for instance, the angina pectoris.[17, 18, 28]

2. *The Disturbance in Carbohydrate Metabolism.*—Statistical proof of the frequent association of temporarily disturbed carbohydrate metabolism and coronary occlusion has been furnished by a number of workers.[29-32] Raab and Rabinowitz[32] found abnormal sugar tolerance curves in all cases of coronary occlusion during the first two weeks of illness. In the present instance the moderate hyperglycemia and slight glycosuria on admission were attributed directly to coronary occlusion. They could have resulted from (a) pain and shock (Levine[29]), (b) reflex spasm of the already diseased pancreatic blood vessels (Cruickshank[33]), or (c) the edema of the medulla and lower pons which Hausner and Hoff[34] have found early in coronary thrombosis. The last mentioned workers believe this transudation produces a disturbance of the vegetative nervous centers of the brain, resulting in glycosuria and hyperglycemia. Later events showed that in our case none of these mechanisms was involved and that the abnormality in carbohydrate metabolism was entirely of pancreatic origin. At autopsy no normal insular tissue could be found. In view of this it is rather remarkable that only twenty-five units of insulin sufficed to keep the patient sugar-free and at one time brought the blood sugar within the range of normal. The concomitant absence of acetonuria and the presence of obesity might suggest a lowered activity of the pituitary gland, which unfortunately could not be investigated post mortem.

3. *The Low Urinary Diastase.*—Whether diastase excretion values are high or low in pancreatic disease would seem to depend chiefly upon the relative degrees of obstruction and necrosis present. High degrees of duct occlusion would naturally produce very high values, whereas advanced destruction would give rise to normal or extremely low values. The significant feature in the present instance seems to be the continuously decreasing value which could be looked upon as a measure of the progression of pancreatic disintegration.

4. *The Role of the Gall Bladder Disease in Precipitating the Acute Pancreatitis.*—Obvious chronic pathologic changes were present in the gall bladder; it seems likely that temporary lodgment of a small stone at the ampulla, associated with heavy eating and drinking, could have initiated the entire disturbance. Some years ago Opie[35] demonstrated the causative role of such an accident. Although the duct of Wirsung could not be isolated with any certainty because of the advanced necrosis, the common bile duct showed inflammatory changes of an acute nature near its entrance into the duodenum. It seems reasonable to suppose, therefore, that the cholecystic disease and the pancreatic necrosis were causally related. The late increase in the icteric index can be accounted for on the grounds of edema accompanying a spreading inflammatory process.

SUMMARY

1. A case of acute pancreatic necrosis presenting impure auricular flutter and fibrillation is reported. The rarity of the condition and its clinical similarity to coronary thrombosis are stressed.

2. The autopsy failed to disclose any organic changes in the heart to account for the arrhythmia; it was probably initiated by reflexes originating within the abdomen.

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Department of Clinical Reports

JUVENILE RHEUMATIC FEVER

Report of a Case in an Infant Two Years of Age

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ALTHOUGH rheumatic fever in infancy is unusual, the literature nevertheless contains a number of reports of authentic cases. Our present views regarding the incidence of first attacks differ considerably from those which were held even a decade ago. As Roth, Lingg, and Whittemore[1] have pointed out, "acute rheumatism in children has its onset at a far earlier age than is generally implied in the literature on the subject. If in coming years our familiarity with the 'minor' symptoms and signs of juvenile rheumatism becomes greater, and if dependable diagnostic tests come to our aid, the disease may be found to have its onset among the earliest diseases of childhood."

CASE REPORT

The patient was a white male child, 32 months of age, the fourth of four living children. None of the other children and neither of the parents had had rheumatic fever. It is perhaps significant that about a year before the patient was born his parents suffered serious financial reverses which forced them to remove to a small, inadequately heated apartment. Throughout her pregnancy the mother was denied all but the bare necessities, and the surroundings were unfavorable for the baby. Nevertheless, he appeared to be unusually well and strong until the onset of his rheumatic fever. He was not subject to colds, had not had tonsillitis, sore throat, or pains in the extremities, and was never listless, pale, or easily fatigued.

When first seen, the patient was acutely ill. He was sitting up in bed gasping for air and breathing very rapidly with a loud expiratory grunt. His face and extremities were cyanotic, cold, and clammy. The child had caught cold for the first time, and had been treated at home for one week prior to his admission, May 5, 1937, to the Orange Memorial Hospital. The diagnoses on admission were (1) bilateral otitis media, (2) pharyngitis, and (3) bronchopneumonia. On May 9, when the patient appeared quite "toxic," hemolytic streptococci were recovered from his throat. At this time the hemoglobin was 60 per cent (Sahli), the erythrocytes numbered 3,240,000, and the leucocytes 14,000, per cubic millimeter, respectively; 62 per cent of the leucocytes were polymorphonuclear cells and 38 per cent were lymphocytes. Roentgenograms taken on admission showed bronchopneumonia, chiefly in the lower lobe of the left lung, and a cardiac shadow the contour of which was suggestive of congenital heart disease. On May 11 the hemoglobin was 55 per cent, the erythrocyte count 2,800,000, and the leucocyte count 17,100; 42 per cent of the leucocytes were polymorphonuclear cells and 58 per cent were lymphocytes. The sedimentation rate was 14 mm. in thirty minutes and 35 mm. in one hour. The urine was normal. On May 14 the temperature was normal and the pulse "somewhat irregular and quite high." There were roentgenographic changes suggestive of miliary tuberculosis, but the Mantoux test was negative in all

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dilutions. On May 17 a transfusion of 120 c.c. of whole blood was given, and the next day the hemoglobin was 68 per cent, the erythrocyte count 3,780,000, and the leucocyte count 9,100. The differential leucocyte count showed 54 per cent polymorphonuclear cells, 44 per cent lymphocytes, and 2 per cent monocytes. On May 20 the temperature was still normal and the pulse somewhat irregular. Roentgenographically, there was continued evidence of miliary tuberculosis, but the bronchopneumonia appeared to be resolving. Stomach washings were examined for tubercle bacilli, but none was found. On May 25 the patient was discharged from the hospital with a final diagnosis of nasopharyngitis and bronchopneumonia. A diet high in calories and vitamins was prescribed.

A month later the patient again became acutely ill, but the clinical aspects of the case now differed considerably from those which had characterized his first illness. He had passed no urine for twenty-four hours. His breathing was labored and rapid (60 respirations a minute) and there was now only a slight grunt. He was not cyanotic, as he had been before, but pale, and his face was somewhat swollen. There was moderate edema of the legs and lower thighs. The abdomen was distended and tympanitic, and the liver was greatly enlarged, extending almost to the symphysis pubis. Many moist râles were heard over both lungs, but there was no dullness to percussion. At the apex of the heart there were loud systolic and diastolic murmurs which were transmitted over the entire precordium and could be heard very distinctly in the left axilla and under the left scapula. In addition, there was a suggestion of a diastolic murmur in the aortic area. No pericardial friction rub could be heard. The vessels of the neck pulsated violently. A poor prognosis was given, and immediate hospitalization advised.

The patient was admitted to the East Orange Homeopathic Hospital June 2, 1937. He was placed in an oxygen tent, his fluid intake was limited to 500 c.c. in twenty-four hours, and he received ammonium chloride (60 grains a day), salyrgan, and codeine every three or four hours when necessary. He began to pass urine almost at once, his liver receded, the edema of his extremities diminished, and his breathing became much easier. After forty-eight hours the ammonium chloride was discontinued, and he was given 2 c.c. of digalen hypodermically three times a day for three days. He also received one more intravenous injection of salyrgan. He responded so well that by June 9 the liver was only about one fingerbreadth below the costal margin, the peripheral edema had disappeared entirely, and the lungs were free of moisture. On June 19, when he walked out of the hospital, he had recovered completely from his cardiac failure, but his heart was still tremendously enlarged (Danzer ratio 0.75). It is noteworthy that his urine had remained normal throughout and that his sedimentation rate had never exceeded 11 mm. in one hour. The hemoglobin varied between 59 and 62 per cent, and the erythrocyte count was about 3,500,000 per cubic millimeter.

The patient's mother was advised to take him to the shore for the summer, to limit his physical exertion, and to give him frequent sun baths and a diet high in calories, vitamins, and iron. These instructions were carried out and he did very well. On his return, September 1, 1937, examination revealed no peripheral edema or other evidence of cardiac failure. The size of the heart had not changed appreciably, and the murmurs were the same as before. The heart sounds were of good quality and sinus arrhythmia was present. The blood pressure could not be measured accurately. There was no dyspnea on moderate exertion. The patient's appetite was excellent, and on the whole he presented a very healthy appearance.

On October 2, 1937, he again caught a "cold" which did not respond to home remedies. Three days later he was readmitted to the Homeopathic Hospital. His face was swollen, his legs were edematous, and his liver extended to the level of the umbilicus. His heart was no larger than it had been a month earlier, and the same systolic and diastolic murmurs were audible over the entire precordium. There was dullness over the middle lobe of the right lung, and both lungs were filled

Fig. 1.—Photograph showing the relative thickness of the musculature of the right and left ventricles, indicating the pronounced hypertrophy of the left ventricle.

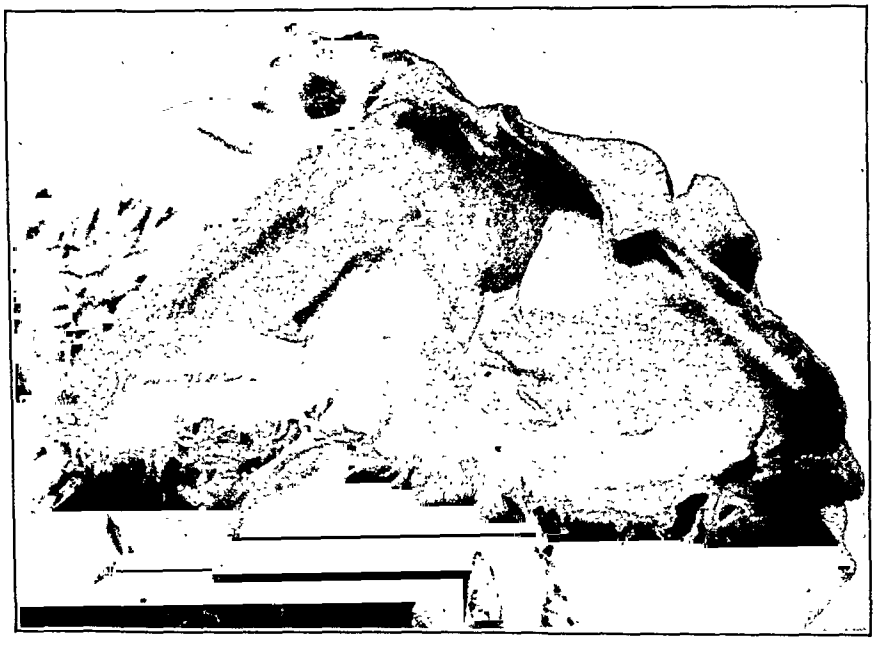

Fig. 2.—Photograph showing the mitral valve and interior of the left auricle. The corrugation of the auricular endocardium (MacCallum lesions), which is typical of rheumatic heart disease, is well illustrated. The shortening of the chordae tendineae and the knoblike thickenings along the valve margin are readily seen.

with moist, bubbling râles, but there was no evidence of free fluid in either pleural sac. He had passed no urine for twenty-four hours. The diagnoses were (1) rheumatic pancarditis with decompensation, and (2) bronchopneumonia. The intravenous injection of 50 c.c. of 25 per cent glucose and 1 c.c. of salyrgan, together with the oral administration of ammonium chloride, proved to be relatively ineffective. A transfusion of 60 c.c. of whole blood was given October 8, but the patient grew worse rapidly and died the next day. Three days before death the urine was essentially normal, the hemoglobin was 52 per cent, the erythrocyte count was 3,400,000 per cubic millimeter, the leucocyte count 15,000 per cubic millimeter; the differential leucocyte count showed 72 per cent polymorphonuclear cells and 28 per cent lymphocytes; the sedimentation rate was 30 mm. in an hour.

At autopsy* the veins of the neck and upper chest were congested, the abdomen enlarged, and the lower extremities slightly edematous. There was no pleural effusion. The entire middle lobe of the right lung, together with the adjacent portions of the upper and lower lobes, was airless and dark brown in color. The left lung was crepitant throughout, but exuded a frothy, bloody fluid. The pericardial sac contained more than the normal amount of fluid. The heart weighed 240 gm., an increase of about 400 per cent. The left ventricle was dilated and its wall was much thicker than normal. The heart muscle was deep red in color and tough in consistency. The free margin of the mitral valve was slightly thickened. The endocardium of the left auricle was somewhat corrugated, but elsewhere the endocardium was normal. The right auricle and ventricle were dilated. The aorta and pulmonary artery were normal.

Microscopic examination showed leucocytic infiltration about the small bronchi. The walls of the alveoli were thickened and fibrous, and the alveoli contained numerous desquamated cells of the type common in heart failure. Granulocytes were present in a few alveoli. Within the interstitial tissue of the myocardium there were inflammatory lesions consisting of round and plasma cells, with occasional giant cells, which were identified as Aschoff bodies. Many of these lesions were seen in relation to small coronary branches.

The final diagnoses were: (1) congestion of the kidneys, (2) congestion of the lungs and chronic interstitial pneumonitis, (3) bronchopneumonia, (4) chronic interstitial rheumatic myocarditis, (5) congestion and hyperplasia of the spleen, and (6) congestion and central necrosis of the liver.

COMMENT

The pathologic process in the lung was very similar to the so-called rheumatic pneumonia. The chronic nature of the pneumonitis and myocarditis warrants the assumption that the rheumatic infection was not of recent origin, and the accompanying photographs (Figs. 1 and 2) tend to substantiate this opinion. The probability is that the onset occurred between the ages of 18 and 24 months.

SUMMARY

A case of rheumatic heart disease in an infant, including necropsy observations, is reported. It is probable that first attacks of rheumatic fever frequently occur at a much earlier age than has been suspected.

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*Performed by Dr. Edward Fendrick.

ACUTE STAPHYLOCOCCIC VALVULITIS WITH VEGETATIONS OF RHEUMATIC TYPE*

Report of a Case

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FOR many years the etiology of rheumatic valvulitis has been a much debated question. Many believe that bacteria are responsible, but others consider the etiology unknown. Only a brief review of the literature is given because comprehensive reviews have recently been made by several writers (Jordan[1]).

Streptococcus viridans has been cultured from the blood stream of patients with rheumatic fever by Poynton and Payne,[2] Rosenow,[3] Swift and Kinsella,[4] Clawson,[5] Cecil, Nicholls, and Stainsby,[6] and others. The positive results have varied with the different investigators. Cecil obtained as high as 83.9 per cent positive results, using a modification of Clawson's technique. Improved technique apparently accounts for the greater number of positive cultures. Some variety of *Streptococcus viridans* is almost always encountered. The variety found most often by Clawson[5] was a type similar to *Streptococcus faecalis*. In seven cases in Cecil, Nicholls, and Stainsby's series[6] the joints were cultured. From five of these, *Streptococcus viridans* was obtained. Cecil believes that the streptococci enter the blood stream and produce septicemia, then localize in the joints in a manner similar to infectious arthritis, as for example, the gonorrheal variety.

Clawson, Bell, and Hartzell[7] have found that typical verrucae of acute rheumatic valvulitis are found in 75 per cent of cases of subacute bacterial endocarditis. They conclude that the larger bacterial vegetations are only a more severe degree of a similar process. This conclusion is based upon the fact that differentiation of borderline cases is difficult both pathologically and clinically. Von Glahn and Pappenheimer,[8] and Gross and Fried[9] agree that both lesions are found on the same valve frequently, but they believe them to be of separate etiology.

Gross and Ehrlich[10] regarded the Aschoff nodule as specific for rheumatic fever. Clawson,[11] on the other hand, found the Aschoff nodule in various conditions, such as puerperal sepsis, syphilis, and subacute bacterial endocarditis. He states that it is most commonly encountered in rheumatic fever but that it may occur in other infectious processes.

Colburn and Pauli[12] give evidence to show that throat infection with hemolytic streptococci is the first step in the rheumatic process. They

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find that the incidence of this throat infection checks with the geographic distribution of rheumatic fever. Studies on agglutinations, complement fixation, precipitin reactions, and antistreptolysins of sera from rheumatic patients also indicate that the hemolytic streptococcus is an important etiologic factor.

Inasmuch as bacteria are not demonstrable in the acute rheumatic verrucae, it has been suggested that rheumatic fever is caused by a virus. Schlessinger, Signy, Amies, and Bernard[13] have obtained what they believe to be elementary bodies from pleural and pericardial exudates of rheumatic patients. These are often agglutinated by the sera of rheumatic patients, especially when the disease is active and advanced. This does not occur in control sera from normals or patients with other diseases. They present two cases in which the serum agglutinated hemolytic streptococci but not the elementary bodies.

CASE REPORT

The case is that of a young man, 21 years old, who was first seen Dec. 11, 1937, complaining of marked pain in the great toe of his left foot. This had started two or three days before. Examination disclosed a bluish-black bullous formation covering the entire tip of the toe. This was surrounded by a narrow, red, inflamed area. The toe was sensitive to touch. He had a similar lesion on the tip of the middle finger of the right hand which had been present since Nov. 20, 1937; he had stuck this finger under the nail with a fork while washing dishes in a cafeteria a few days before. The infected area had drained three or four times and closed again. No drainage had occurred for three or four days, and during this time the toe had become sensitive.

He was sent home and advised to apply warm boric packs. Until this time he had felt well, having no complaints other than those referable to his toe and finger, and had continued his work.

Late the same afternoon, December 11, he became sick with headache, chills, sweats, and aching all over his body. He said he felt as if he were coming down with the grippe. That evening he had a temperature of 101° F. by mouth, a pulse rate of 110, generalized aching, nausea, and a moist warm skin. On December 12 the findings were the same except that he complained of more pain in his toe. His temperature was 101.4° F. and pulse rate, 110.

On December 13 he was very ill and was hospitalized. His temperature was 101.8° to 104.4° F. and pulse rate, 120 to 126. He became very restless and almost irrational at times. The skin was dry. The body, especially the extremities, was very sensitive to touch; he would cry out if an extremity was moved. There were two purplish-red papules about 5 mm. in diameter on the dorsum of the right forearm, and another in the right posterior lumbar region. He coughed often and had difficulty in clearing his throat. The sputum was often bloodstreaked. The pupils reacted to light. The throat was clear. There were no murmurs or thrills over the precordium. The lungs showed nothing abnormal. The liver was palpable 2 cm. below the costal margin and felt soft and tender. There was definite rigidity of the neck. Spinal puncture revealed a slightly turbid fluid under increased pressure. Thirty cubic centimeters of antimeningococcic serum were given intraspinally and 30 c.c. intravenously. About 11:00 P.M. a red papular rash appeared, covering both shoulders and the back.

The urine was amber colored, cloudy, and acid in reaction. Its specific gravity was 1.016. It contained a moderate amount of albumin (++), but no sugar. Micro-

scopic examination showed two hyaline casts, eight to ten granular casts, and two to five pus cells per low-power field. The leucocyte count was 10,800, of which 4 per cent were promyelocytes, 6 per cent myelocytes, 34 per cent stab forms, 52 per cent mature polymorphonuclear cells, and 4 per cent lymphocytes. A shift to the left was noted. No pneumococci of Types I, II, III, V, or VII could be found in the sputum. The sputum was bloody and contained numerous gram-positive cocci in pairs and chains. The spinal fluid contained a trace of globulin (Nonne-Apelt reaction) and sixty cells per cubic millimeter, but no organisms were found on smear. Roentgenologic examination of the chest revealed no positive changes.

On December 14 the patient was weaker and irrational. His body was very sensitive, and his neck was rigid. There were purplish-red nodules, 3 to 5 mm. in diameter, on the extremities and back. For the first time a soft to-and-fro murmur was heard over the fourth intercostal space, halfway between the sternal border and the nipple line. It radiated up to the third interspace, down to the fourth, and to the left of the nipple line. It could not be heard in the axilla. There was also a friction rub over the apex, best heard at the fifth rib, radiating down to the fifth intercostal space and to the left as far as the nipple line. The temperature was 103° F. in the afternoon, 102° F. at midnight. A blood culture, taken December 13, showed pure *Staphylococcus aureus;* there were over 200 colonies on the plate (a little more than 1 c.c. of blood was used). The blood Wassermann reaction was negative. Prontylin was given by mouth, and bacteriophage was given intramuscularly.

On December 15 his condition became very poor; his pulse was weak, and he was irrational and had urinary incontinence. He was given 300 c.c. of blood by vein. The systolic and diastolic murmurs were somewhat louder. The friction rub was coarser and extended up to the third rib. The temperature in the morning was 102° F., and in the afternoon 101° F.

On December 16 he was very irrational. The temperature rose to 105° F. at 4:00 P.M. with a respiratory rate of 38. Prontysil was given intraspinally and intravenously. The systolic and diastolic murmurs were more pronounced than on the preceding day. The friction sound became rough, loud, almost leathery, and was audible over the entire precordium. He was placed in an oxygen tent at 8:00 P.M. when it was discovered that he was becoming increasingly cyanotic. The temperature rose to 107° F., and he expired at 2:38 A.M., December 17.

The patient had always been in excellent health prior to the present illness except for the usual childhood diseases. He had bronchopneumonia at the age of 7 years, tonsillectomy at 7 years, chicken pox, measles, mumps, and whooping cough at the age of 10 years. He worked in a Civilian Conservation Corps camp during the summer of 1934 and was found normal on physical examination. He entered the University of Minnesota in September, 1934. The Health Service examination on entrance showed nothing abnormal.

On October 9, 1937, he was examined by Dr. Weisman for pain in the right lower abdomen. Nothing was found except an enlarged right inguinal ring. At that time he was working as a tinsmith and doing some very heavy lifting. No murmurs were present and the lungs were negative. The urine was normal and the leucocyte count was 7,750. He had never had any ailment similar to rheumatism, chorea, or growing pains. There was no history of chronic sore throat or of scarlet fever.

At autopsy the body was found to be well nourished and well developed, showing cyanosis, icteric sclerae, and petechiae over the neck, chest, arms, and legs. There was no edema. The left great toe was swollen and ecchymotic, with no ulceration. The right great toe had a similar appearance in a less degree. The tip of the middle finger of the right hand was swollen and ecchymotic, with no break in the epithelium.

The pericardial sac contained about 100 c.c. of seropurulent fluid. The serous surfaces were completely covered by a fibrinous exudate. The heart weighed 385 gm. and showed moderate dilatation of all four chambers with no gross hypertrophy. A continuous row of small white vegetations was found at the closure line of each mitral leaflet (Fig. 1). They were globular with smooth surfaces and were the typical verrucae of acute rheumatic valvulitis. However, some showed a fuzzy surface and were a little larger. This suggested the coexistence of bacterial lesions. There was no thickening of either leaflet other than that produced by the vegetations just mentioned. The other valves and the mural endocardium showed nothing of note. There was a small abscess in the interventricular septum and another in the left ventricular wall near the apex. The myocardium showed cloudy swelling.

Each lung was markedly congested and showed small areas of suppuration.

Fig. 1.—Row of vegetations on auricular surface of mitral leaflets. Photograph.

The spleen weighed 425 gm. An abscess 2.5 cm. in diameter was found; the remaining pulp was very soft.

Multiple small abscesses were found throughout the liver, which weighed 2,050 gm. Abscesses and septic infarcts were seen in each kidney, and there was also bilateral pyelitis. The mucosa of the pelves, ureters, and bladder was stained pink.

An abscess 4.5 cm. in diameter was found in the left frontal lobe of the brain with several small abscesses in the cerebral cortex bilaterally. There were small areas of suppuration on the superior surface of the brain. The spinal cord appeared normal.

A stained smear from the verrucae on the valve revealed staphylococci.

Microscopic study of the various organs revealed nothing of note except abscess formation together with clumps of gram-positive cocci. Acute inflammation of the meninges of the spinal cord was present. The majority of the vegetations on the

mitral valve were definitely rheumatic in type; there was a typical proliferative reaction with large oval nuclei and a somewhat basophilic cytoplasm; there was definite palisade arrangement of the cells. The surface endothelium was intact;

Fig. 2. Fig. 3.

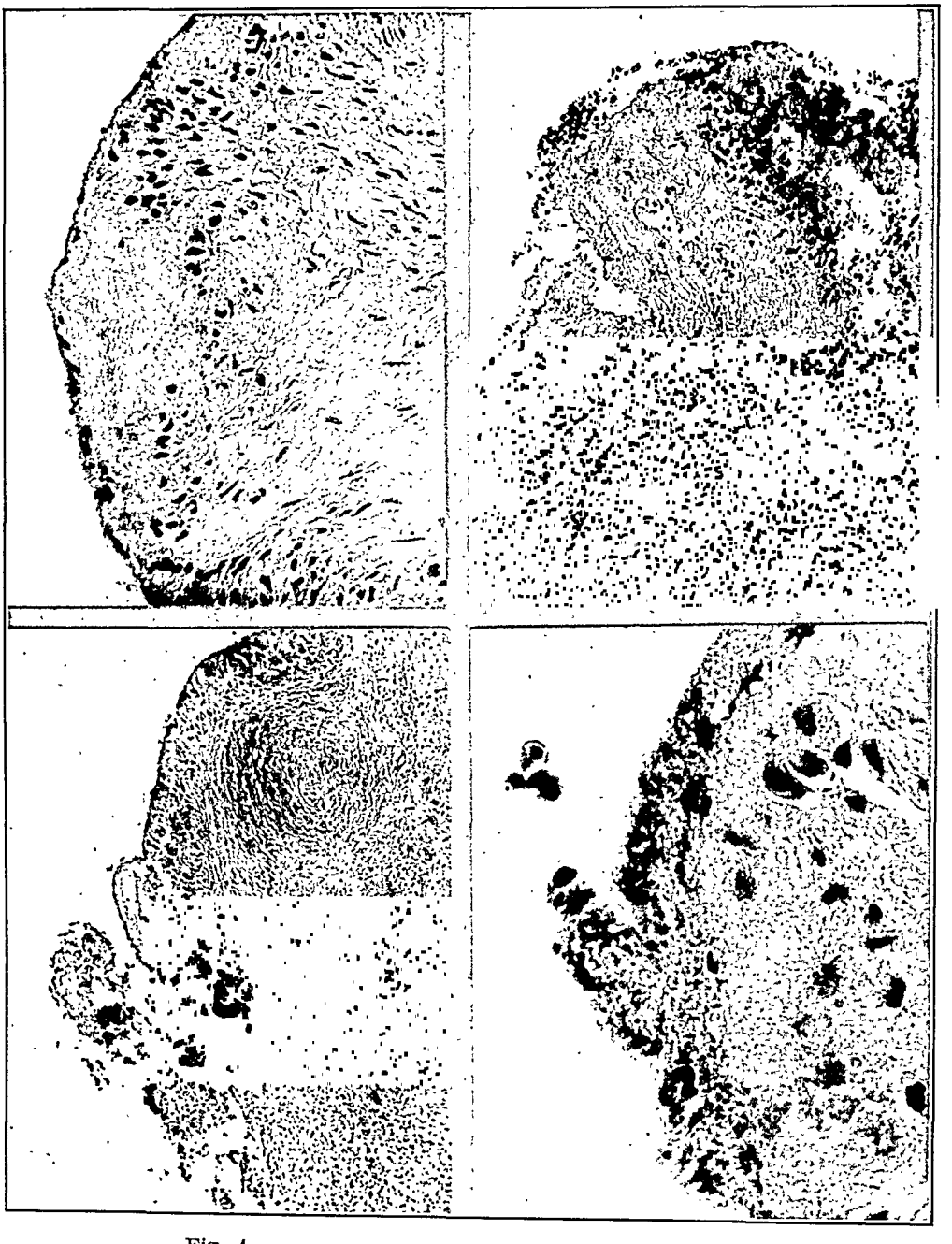

Fig. 4. Fig. 5.

Fig. 2.—Typical rheumatic vegetation. Note the hyaline necrosis under the intact endothelium. Photomicrograph.

Fig. 3.—Bacterial type of vegetation. Photomicrograph.

Fig. 4.—Transitional variety of vegetation; bacterial portion on left, rheumatic on right. Photomicrograph.

Fig. 5.—Transitional type of vegetation. Note rheumatic structure and bacteria near the surface. Gram stain. Photomicrograph.

under this there was a moderate amount of hyaline necrosis (Fig. 2). Some of the larger vegetations were composed of platelet material with numerous gram-positive cocci toward the surface and with a collection of polymorphonuclear cells at the base (Fig. 3). Other vegetations showed transitions between the rheumatic and the bacterial variety. Some were seen in which one part was typically rheumatic and an adjacent part was a bacterial lesion (Fig. 4). Others had a typical rheumatic structure except for the presence of bacteria near the surface. It may be that the last two varieties of vegetations were transitional forms (Fig. 5).

An acute polymorphonuclear exudative reaction was present in the mitral, tricuspid, pulmonary, and aortic rings. In the first three rings the inflammation was of a rather severe degree, more so than in the aortic ring. The pulmonary and tricuspid leaflets were acutely inflamed, the exudate being composed mostly of polymorphonuclear leucocytes. The cusps of the aortic valve were not involved.

A few small abscesses were present in the myocardium, many of which contained masses of staphylococci. There was a mild perivascular reaction composed mostly of polymorphonuclear cells. There were no Aschoff bodies.

Microscopic evidence of old rheumatic disease in the heart could not be found. The stigmata of old rheumatism described by Gross were not present. The pericardium showed acute fibrinous pericarditis and no evidence of past rheumatic disease.

DISCUSSION

In many cases of acute rheumatic endocarditis Clawson, Bell, and Hartzell[7] found vegetations on the valves that were identical microscopically with those of bacterial endocarditis. They insist that there are many transitions between rheumatic and bacterial vegetations on the same leaflet.

The history in this case indicates that a staphylococcic pyemia occurred, during the course of which signs of cardiac involvement appeared. There was no clinical evidence of a preceding acute rheumatic endocarditis. At autopsy the valve leaflets showed both typical rheumatic and typical bacterial vegetations with many transitional forms.

Two interpretations are possible: (1) A staphylococcic infection developed and produced lesions of both rheumatic and bacterial types as well as intermediate forms; (2) the patient had acute rheumatic endocarditis without clinical symptoms, and a staphylococcic infection was then superimposed which gave rise to bacterial vegetations. The numerous transitional vegetations seem to favor the first explanation.

SUMMARY

A case of staphylococcic pyemia is presented which showed many rheumatic, some small bacterial, and some transitional forms of vegetations on the mitral valve. It is suggested that vegetations of rheumatic type may be produced by staphylococci.

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Department of Reviews and Abstracts

Selected Abstracts

Katz, L. N., and Mendlowitz, M.: Heart Failure Analyzed in the Isolated Heart Circuit. Am. J. Physiol. 122: 262, 1938.

A single isolated heart circuit is described for the study of the dynamics and energetics of spontaneous heart failure.

It is possible in this preparation to permit failure to occur with little or no change in total diastolic volume.

With the development of heart failure and with a relatively unchanged diastolic volume, there is a progressive decrease in the work and oxygen consumption of the heart and little change in its mechanical efficiency.

When the work of the heart is kept constant, no change in oxygen consumption or mechanical efficiency occurs, despite a progressive increase in the diastolic volume and the left auricular pressure.

These experiments demonstrate that heart failure must be defined in terms of a single chamber, rather than the heart as a whole.

It is concluded that failure of a heart chamber is due to an increase in load, a decrease in contractile power, or both, of such a degree that the chamber begins to fail to do the work imposed upon it by the load.

It is shown that loss of contractile power is manifested by a reduction in total energy release and hence work at a given diastolic volume and (except terminally) not by a decrease with which the liberated energy is utilized for mechanical work.

AUTHOR.

Karasek, F., and Poupa, O.: Seasonal Variations in the Sensitivity to Adrenalin of the Muscular Arteries of *Rana temporaria*. Compt. rend. Soc. de biol. 126: 113, 1937.

The authors demonstrate by direct measure of the diameter of the lingual artery of the frog that it is more sensitive to adrenalin in the winter than in the spring and, more interesting still, find that in the female a marked loss of sensitivity occurs immediately after spawning.

STEELE.

Karasek, F., and Poupa, O.: Augmentation of the Vascular Effect of Adrenalin by Testosterone. Compt. rend. Soc. de biol. 126: 116, 1937.

In the manner just described the tests show that three days after injection of 1 mg. of testosterone (perandren, Ciba) the lingual artery of the frog is more sensitive to adrenalin, and the authors state that in press is a similar piece of evidence presented by them, that folliculin also increases the sensitivity to adrenalin markedly.

STEELE.

Karasek, F., and Poupa, O.: Modification of the Vascular Effect of Adrenalin by Hormones of the Opposite Sex. Compt. rend. Soc. de biol. 126: 118, 1937.

Using the same method the authors show that sex hormones of the opposite sex (testosterone in females, folliculin in males) gives rise to a decrease rather than an increase in sensitivity of the lingual artery of the frog to adrenalin.

STEELE.

Fleisch, A.: Concerning a Vasodilator in Erythrocytes. Arch. f. d. ges. Physiol. 239: 345, 1937.

Hemolyzed red blood cell corpuscles obtained from the rabbit, dog, ox, and cat were found to have a marked effect upon increasing blood flow and lowering pressure in cats and rabbits. The author believes that a ferment present in the blood destroys the substance because in two hours the effect is more than half gone and because preserving the blood at 0° C., or with hydrocyanic acid 1/10,000 and heating prevents destruction of the substance. The substance is not soluble in ether, chloroform, or acetone, but is readily soluble in water. From biologic tests of its action upon various types of smooth muscle, he concludes that the substance is not acetylcholine, histamine, adenosin, or adenylic acid.

STEELE.

Fleisch, A., and Weger, P.: On the Appearance of Vasodilator Substances in the Blood. Arch. f. d. ges. Physiol. 239: 354, 1937.

Using the two hind legs of a dog—one as "donor," in the circulation of which a Stromuhr and a cannula for removing samples of venous blood were placed, the other as "recipient," furnished with a pressure perfusion apparatus—venous samples of blood from one leg could readily be perfused through the other under various circumstances. Increase in flow through the perfused leg was taken as evidence of a vasodilator substance in the venous blood of the other leg. The authors found that under normal resting conditions almost no vasodilator substance was present in the venous blood but that after muscular work (electrical stimulation of the muscles of the donor leg) and with insufficient circulation large amounts could be shown to be present.

STEELE.

Fleisch, A., and Weger, P.: Vasodilatory Action of Phosphorrelated Metabolic Products. Arch. f. d. ges. Physiol. 239: 362, 1937.

The hind legs of dogs were perfused in the manner described in the previous paper with blood to which was added numerous phosphoric acid compounds, and their effect compared with histamine and acetylcholine. Adenosin triphosphoric acid was found to be the most powerful vasodilator of all the phosphoric acids used, being active in 100 times greater dilution than the nearest competitor, muscle adenylic acid. The authors conclude, although the reasons are not quite clear, that the sum of the actions, all the intermediate products of metabolism, acetylcholine, adenosintriphosphoric acid, histamine, constitute an adequate stimulus for the vasodilatation which follows exercise.

STEELE.

Böger, A., and Wezler, K.: Calculation of Total Peripheral Arterial Resistance in Man. Arch. f. exper. Path. u. Pharmakol. 186: 43, 1937.

The calculations are based upon the conception that arterial elasticity is as important as degree of contraction of arterioles in forming peripheral resistance.

He derives a formula which takes, he believes, better account of both these factors than a somewhat similar one of Broemser and Ranke's. The formula is $w = \left(\frac{Pd}{\Delta p} + \frac{h}{H}\right)\frac{E'\tau}{2}$ in which w is the functional resistance in dyne seconds per cm^5, $\left(\frac{Pd}{\Delta p} + \frac{h}{H}\right)$ an expression which serves to calculate mean pressure *(Pm)* by integration of the pulse curve based upon absolute pressures measured by a cuff and Korotokoff sounds, E' a coefficient of elasticity τ the duration of the pulse cycle. The present authors arrive at figures somewhat lower (roughly two-thirds) than Broemser and Ranke and show that the difference is chiefly due to the fact that the former workers calculated from the run off during diastole only, a period during which resistance is greater than during systole. Their normal average is given as 1842 dyne seconds per cm^5, about halfway between that of Frank and that of Broemser and Ranke. They point out that for some purposes the total average resistance, rather than that of a particular region, is an important conception.

STEELE.

Wezler, K., and Böger, A.: The Total Arterial Resistance Under Various Kinds of Sympathetic Stimulation. Arch. f. exper. Path. u. Pharmakol. 187: 65, 1937.

In these studies the authors used their published method of calculating total peripheral resistance—a physical method dependent upon integration of pulse curves referred to absolute levels of pressure obtained by the usual auscultatory method and designed to account for elastic as well as frictional resistance. They investigated the effect upon this resistance of various sorts of sympathetic stimulation. With suffocation (holding the breath for 20-40 sec.) and on plunging the arm into a water-bath at 2° C. for 40 to 90 sec., rises of total resistance of from 50 to 100 per cent were regularly observed. Injection of sympathol was also followed by increased resistance, but adrenalin was, in contrast, followed by decreased total resistance. The most marked *decrease* (to one-fourth or to one-fifth the resting value) in total resistance was observed during recovery from strenuous muscular work. A method is appended for calculation of regional variations in resistance.

STEELE.

Spanner, R.: Circulatory Shunts in the Human Kidney; a Contribution to Knowledge of the Distribution of the Load Throughout Its Vascular System. Klin. Wchnschr. 162: 1421, 1937.

There are three sites, according to Spanner, in the kidney where arterial blood can be shunted in considerable quantities directly to the venous side without traversing the glomerular and tubular vascular network. The first occurs in the small calices of the pelvis all over the wall where he could count as many as 18 arteriovenous anastomoses in 5 sq. mm., and in certain areas where there are "venous nests" as many as 23 in 2 sq. mm. The second site is in the cortex. He states that for years he has noticed that before 12 or 15 c.c. of a variety of materials is injected into the arteries, it can be found in the veins. Moreover, when he injects intra-arterially 30 per cent solution of kaolin-gelatin—a material which if not too warm, does not ordinarily pass through capillaries—it too can be found in veins. In cleared preparations it appears that the anastomosis here is between the lobular arteries and veins. The third place is in the capsule where the arteriovenous anastomoses occur in several ways, chiefly, capsular arteries to lobular veins and lobular arteries to capsular veins. The capsular vessels are derived from extrarenal sources. He promises a longer description soon.

STEELE.

Van Liere, Edward J., and Sleeth, Clark K.: Cardiac Hypertrophy During Pregnancy. Am. J. Physiol. 122: 34, 1938.

The normal heart weight-body weight ratio in 90 normal adult female guinea pigs was found to be 3.17 grams per kilogram. Twenty-six animals were killed within seventy-two hours after they had given birth to their young; the HW/BW ratio in these animals was found to be 3.06. Twenty-seven pregnant animals were killed during the latter part of pregnancy and the HW/BW ratio was found to be 2.93. After the weight of the uterine contents had been subtracted from the body weight, however, the HW/BW ratio was found to be 3.17, that is, exactly the same as in the control animals. Corroborative data were also obtained from ten cats and seven dogs.

The conclusions drawn from this work are: 1. Pregnancy does not cause cardiac hypertrophy in the guinea pig. (Nor was there any evidence of cardiac hypertrophy in 10 pregnant cats and 7 pregnant dogs.) 2. Since pregnancy does not produce cardiac hypertrophy in three different types of animals, it seems doubtful that it would produce it in human beings. 3. Increased cardiac work does not necessarily produce cardiac hypertrophy.

AUTHOR.

Moritz, Alan R., and Atkins, Joseph P.: Cardiac Contusion: An Experimental and Pathologic Study. Arch. Path. 25: 445, 1938.

The objective pathologic criteria for distinguishing between a cardiac contusion and a cardiac infarct vary in usefulness according to the age of the lesion. In the case of a recent myocardial lesion, the only evidence that should almost invariably serve to identify an otherwise indeterminate injury as an infarct is the finding of recent coronary occlusion. Pathologic changes more likely to be found in early contusion than in early infarction include massive interstitial hemorrhage, laceration, and tissue disorganization. Since all of these changes may be seen following spontaneous rupture of an early infarct, they are not conclusive. In the case of an older myocardial lesion there is no means of distinguishing objectively between contusion and infarction. Deposits of hemosiderin in myocardial scars are more likely to be seen in healed contusions than in healed infarcts, but, since hemosiderin is seen occasionally in healed infarcts, its presence is not conclusive. Three months after injury hemosiderin is found infrequently in traumatic scars, so that its absence in no way excludes the possibility of a lesion having been of traumatic origin. The presence or absence of remote coronary occlusion does not serve to identify a myocardial scar as having resulted from infarction or contusion, inasmuch as a heart which is the seat of occlusive coronary disease may have a superimposed traumatic lesion, and a heart with a large healed infarct may have no demonstrable coronary occlusion. The pathologic characteristics of the scars of myocardial contusion and infarction are frequently identical, and the presumptive nature of their origin must be determined by historical data rather than by post-mortem examination.

AUTHOR.

Holbrook, Arthur A.: Normal Venous Pressure as Determined by a Direct Method. Am. J. M. Sc. 195: 751, 1938.

Normal venous pressure values obtained by various direct methods are quoted from the literature.

Venous pressures of 48 normal subjects determined according to the method of Griffith, Chamberlain, and Kitchel are presented in three tables. The first series was studied with the test arm "extended by the side in supination." In the second and

third series, the arm was abducted to at least a 70-degree angle and supported approximately as originally described by Moritz and Tabora. It was demonstrated that this single change in a technical detail accounted for greater accuracy in obtaining readings, more consistent results, and a lower range of venous pressure values.

Details of the technique used are given.

The normal range of venous pressure thereby obtained in 35 cases was from 10 to 100 mm. of physiologic saline solution, the average value being 65 mm. The older age group tended to have lower levels than the younger.

AUTHOR.

Fraser, Francis R.: The Clinical Aspects of the Transmission of the Effects of Nervous Impulses by Acetylcholine. Brit. M. J. 1: 1249, 1293, 1349, 1938.

(The Croonian Lectures delivered before the Royal College of Physicians of London.)

The acceptance of acetylcholine as the transmitter of the effects of nervous impulses throughout a large part of the peripheral nervous system has been followed by important advances in knowledge of the physiology of the autonomic nervous system and of voluntary muscle and neuromuscular stimulation. Already, in the few years since the principle gained general acceptance, a number of aspects of clinical value have emerged.

Many of the long-established therapeutic uses of atropine and physostigmine are explained.

Two new substances of therapeutic value have been introduced to clinical medicine—doryl and mecholine—and their value in the treatment of intestinal distention and atony, of postoperative and post-partum retention of urine, and of supraventricular paroxysmal tachycardia has been established.

A third new substance, prostigmin, has an established therapeutic value in the treatment of intestinal distention and atony and has so dramatic an effect on the muscle weakness and fatigue in myasthenia gravis that it has altered the outlook for patients suffering from this disease, and this therapeutic effect is of diagnostic value.

This action of prostigmin has led to an analysis of the cause of the muscular disability that seems likely to solve the problem of the cause of the disease.

Of greater importance, I believe, will be the discoveries that acetylcholine transmission will bring about in the future, for all processes, tissues, and organs of the body are affected by it. Further advances in pharmacology may be expected, for acetylcholine lends itself readily to modifications by the synthetic chemist. Emotional disturbances have been linked with skin lesions through acetylcholine, and observations have been recorded that must lead to a better knowledge of the functions of the central nervous system. And if acetylcholine transmission should be proved to occur there as well as in the periphery, still further advances in knowledge of clinical importance may be expected.

AUTHOR.

Benjamin, Julien E., Landt, Harry, and Culver, Laurence R.: The Body as a Volume Conductor and Its Influence on the Electrical Field of the Heart. Am. J. M. Sc. 195: 759, 1938.

Visual evidence is presented to confirm the accepted fact that the extremities act as volume conductors of the electrical potential generated in the heart.

The lungs transmit none of the differences in electrical potential registered in the electrocardiograms obtained by surface leads.

The lung pedicles act as the sole bridge for transmission of current to the lungs. These pedicles offer selective pathways of conduction.

The recent controversies as to the advisability of using the apex of the heart or the fourth interspace just to the left of the sternum for the site of preference of the right arm electrode in Leads IV and V, seem to accept, a priori, the dictum that the chest is a volume conductor. We are convinced that the descrepancies seen in these controversies can be explained on the basis that the chest is not a volume conductor.

AUTHORS.

Schlomka, G., and Witzenrath, W.: The Determination of the Relative Duration of Systole. III. Relative Systolic Duration in the Presence of Inverted T-Waves. Ztschr. f. Kreislaufforsch. 30: 281, 1938.

In 140 cardiac patients the duration of systole relative to the cycle length was measured. It was found that the presence of an inverted $T_{1 \text{ and } 2}$ (in 76 of them) did not shorten the relative duration of systole; in fact it tended to lengthen it.

KATZ.

Pines, Ign.: A Case of Functional Bundle Branch Block During Pregnancy. Wien. Arch. f. inn. Med. 32: 129, 1938.

The author describes a case of functional bundle branch block of the type known as that of Wolff, Parkinson, and White, which was observed during pregnancy. During this period one has to treat frequent attacks of paroxysmal tachycardia and paroxysmal fibrillation of the auricles. The attacks are interrupted by intravenous injection of ouabain and 20 seconds later pressure on the sinus caroticus. As a prophylactic the author has used with good result the composition of gynergen with quinidine and bromata. It is stated that functional bundle branch block does not lead to greater troubles during pregnancy than the simple paroxysmal tachycardia, provided that this block is not combined with any organic heart disease. As a consequence it is concluded that the functional bundle-branch block is not an indication for the interruption of pregnancy. The article contains also discussion of existing theories. The theory of Wolff, Parkinson, and White, the theory of H. Lohr, and the proposition of C. J. Rothberger are alike rejected with short justification. The theory of Holzmann and Scherf and Wolferth and Wood is also not accepted on anatomical, physiologic, and electrocardiographic grounds. The author believes that the cause of shortening of PR-distance in electrocardiogram is the shifting of pacemaker from sinus to the node of Aschoff-Tavara, as was thought by Wilson. The author is of the opinion that the functional bundle branch block is the result, not of the retardation of conduction of impulses through one of the bundle branches, but of acceleration in the other. On the basis of the appearance of many ventricular extrasystoles in his and other cases, he proves that one of the bundle branches has greater excitability than the other. As it is known that conduction of impulses is closely related to the excitability, one can admit that in functional bundle branch block one of the branches conducts more quickly than normal and more quickly than the other branch. At the end of the article the good result attained with gynergen in the prophylaxis of attacks is explained by the action of gynergen on the thyroid gland.

AUTHOR.

Block, C.: Heart Involvement and Electrocardiographic Findings in Anemia. Acta med. Scandinav. 93: 543, 1937.

Individuals with anemia having marked cardiac symptoms, cardiac pain, and electrocardiographic changes in four leads (viz., low "voltage," depression of S-T segment and low or inverted T-waves) are not necessarily primarily cardiac patients since these symptoms and signs can be produced by the anemia and can disappear as the patient's anemia is improved. This study is based on the analysis of 88 anemic patients. The anemia is not always responsible for the cardiac symptoms and signs since they do not disappear as the anemia disappears.

KATZ.

Rytand, David A.: The Renal Factor in Arterial Hypertension With Coarctation of the Aorta. J. Clin. Investigation 17: 391, 1938.

A consideration of hydrodynamics indicates that the arterial hypertension which is present in the upper part of the body in coarctation of the aorta may not be explained upon the purely mechanical grounds of obstruction to blood flow. In this condition there is an increased resistance in the smaller vessels (arterioles) which receive blood from the aorta proximal to the stenosis of its isthmus. The cause of this localized increased resistance is the same as the cause of the generalized increased resistance in a Goldblatt dog (with partially occluded renal artery); that is, interference with blood supply to the kidneys.

This conclusion is supported by the production of hypertension (cardiac hypertrophy) in rats by partial occlusion of the aorta proximal to one or both renal arteries. With partial occlusion of the aorta between the renal arteries, hypertension occurs only when living renal tissue is present distal to the occlusion; after simultaneous distal nephrectomy, hypertension never occurs even though there exists the same degree of mechanical obstruction to blood flow offered by the stenosis and presence of a collateral bed.

AUTHOR.

Gouley, Benjamin A.: The Evolution of the Parenchymal Lung Lesions in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion. Am. J. M. Sc. 196: 1, 1938.

The characteristic pneumonopathy of acute rheumatic fever can be identified as the precursor of an equally characteristic pulmonary change seen often in chronic rheumatic heart disease.

An intervening subacute stage is featured, as is the late chronic stage, by impaired elasticity of the lung tissue.

Histologic studies indicate that this pulmonary lesion is a chronic interstitial pneumonitis, which, like rheumatic myocarditis, is often accompanied by evidence of recurring inflammation.

One of its characteristic features is a hyperplasia of elastic tissue probably indicative of hypertensive strain in the fine pulmonary circulation.

This pulmonary change is not directly dependent on the presence of passive congestion or of mitral stenosis, since both of those factors may be absent or developed in variable degree. Passive congestion undoubtedly intensifies the interstitial fibrosis, but remains in our opinion a secondary factor.

AUTHOR.

Gouley, Benjamin A.: The Role of Mitral Stenosis and of Post-Rheumatic Pulmonary Fibrosis in the Evolution of Chronic Rheumatic Heart Disease. Am. J. M. Sc. 196: 11, 1938.

The author discusses the probability that: (1) mitral stenosis in some patients is in itself not the sole or possibly even an important factor in the causation of the chronic right heart failure which characteristically terminates chronic rheumatic heart disease; (2) such failure may occur even in the absence of significant mitral valvular dysfunction; (3) the key lesion in this particular type of patient is the association of an intrapulmonary lesion with right ventricular strain; (4) the intrapulmonary lesion is a diffuse fibrosis that at least in its beginning is a direct result of rheumatic pneumonitis; (5) the factor of passive pulmonary congestion becomes important with the development of left ventricular failure which may or may not occur.

AUTHOR.

Wallgren, Arvid: Rheumatic Erythema Nodosum. Am. J. Dis. Child. 55: 897, 1938.

Rheumatic erythema nodosum should be sought among those who react negatively to tuberculin. To prove erythema nodosum is due to rheumatic fever when a tuberculous infection is present at the same time is hardly possible, considering the connection that has been shown to exist between tuberculosis and erythema nodosum. But that does not signify that an erythematous eruption in a tuberculous child must have been produced by tuberculosis.

One may consider rheumatic fever as the cause of erythema nodosum only on condition that the child is not infected with tuberculosis. It is essential that a child be examined for tuberculosis when he has acute rheumatism during which erythema nodosum appears.

MCCULLOCH.

Seely, Hall: Primary Obliterative Pulmonary Arteriolar Sclerosis. J. A. M. A. 110: 792, 1938.

This case is the only one of its kind in a series of more than 3,800 autopsies at the New Haven Hospital. Its infrequence is attested by McCallum in a report of a similar case, the only one in a series of 12,000 autopsies at Johns Hopkins Hospital. If Ayerza's disease is primarily a syphilitic pulmonary arteritis or a syphilitic bronchitis (the two concepts of Ayerza's two most interested pupils), the present case is not one of Ayerza's disease. The Wassermann reaction was negative. The lumina of the pulmonary arterioles were greatly reduced by fibrotic changes, with no evidence of inflammatory reaction. Arteriolar changes such as described in the lung were found in no other tissue. The bronchial mucosa was smooth and shining, and free from exudate or obstructive lesions. Marked eccentric hypertrophy and dilatation were found limited entirely to the right ventricle. The aortic and pulmonary cusps appeared intact and competent. Symptoms of cardiac decompensation were of one month's duration. The patient was not clearly polycythemic but was markedly cyanotic. On admission to the hospital she did not appear acutely ill but died rather suddenly on the third day. No evidence of disease of the coronary arteries or of the myocardium was found at post-mortem examination.

MONTGOMERY.

Lewis, W. H., Jr.: Changes With Age in the Blood Pressure in Adult Men. Am. J. Physiol. 122: 491, 1938.

There has been no satisfactory statistical analysis of the blood pressures in later life, particularly after the age of 60 years. This study has been carried out in order to obtain further information as to the change in blood pressure incident to increasing age. One hundred healthy men, aged from 40 to 89 years, have been studied. Measurements of the blood pressure were made with a mercury manometer by the auscultatory method. Blood pressures were taken in the basal state in the morning after fasting for fourteen hours. The data have been statistically analyzed, and the results indicate that the systolic blood pressure rises continuously after the age of 40 but the greatest rise occurs after the age of 65. Between the ages of 40 and 65 there is an average increase of only 8 mm. in the twenty-five-year span, whereas between the ages of 65 to 90 there is an average increase of 34 mm. The mode of the systolic blood pressure, of the mean, and of the pulse pressures increases with age. The average diastolic blood pressure varies slightly in succeeding decades, but there is no significant increase with age as in the systolic blood pressure. This is in accord with the general view that the diastolic blood pressure level is unaffected by age.

HINES.

Glenn, F., Child, C. G., and Page, I.: The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs. Am. J. Physiol. 122: 506, 1938.

In order to determine, if possible, the relationship between the central nervous system and experimental hypertension, hypertension was produced by the Goldblatt method in five dogs, and the cord was destroyed below the level of the fifth cervical vertebra. Daily blood pressure observations were made over a control period of two weeks, using a van Leersum carotid loop, and hypertension was produced by the application of Goldblatt clamps to the renal arteries. Following this, daily blood pressure observations were made for one month or more, and, if the blood pressure remained elevated, a laminectomy was performed and the spinal cord was sectioned in the low cervical region. Daily blood pressure readings were again obtained until the animal was killed. In all the dogs the destruction of the spinal cord was followed immediately by a sharp fall in blood pressure to below previous normal levels. The blood pressure subsequently returned to a level above the previous normal readings for the animal but did not return to the previous maximal hypertension levels and tended to fall towards the end of the period of observation.

HINES.

Seiro, V.: Concerning Blood Pressure and Circulation in Varicose Veins of the Lower Extremities. Acta chir. Scandinav. 80: 41, 1937.

The author has investigated pressure in the cutaneous veins in the lower limbs. Individuals with varicose veins as well as normal persons were studied. He found that the level of the fluid in the manometer rose usually to the level of the heart, occasionally somewhat lower. The pressures were approximately similar in persons with and without varices. The absolute pressure in the manometer depends on the site of the puncture and the height of the subject. The main factor in production of venous pressure in a person standing at ease is undoubtedly hydrostatic pressure, but certain physiologic activities, respiration and muscular activity of the limbs, cause it to vary. Deep inspiration or activity of

the muscles in the limbs lowers the pressure; deep expiration raises it. If the valves are intact, the fall is considerable, if incompetent the fall is less noticeable. But if, in the latter case, the vena saphena magna is compressed above the site of puncture, and the subject makes continuous walking movements, the pressure falls nearly to the same degree as for intact valves. This supplies us with a surer method of ascertaining the competency of the valves. Simultaneous measurement of pressure in the deep and superficial veins lead the author to conclude that the blood in the venous circulation of the lower limbs flows from the cutaneous veins through the anastomosing vessels into the deep veins and leaves the limbs through the latter. This is certain during muscular activity and is probably true for the erect posture.

STEELE.

Slany, A.: The Relation of Anomalies of the Circle of Willis to the Formation of Aneurysms in Vessels at the Base of the Brain. Virchows Arch. f. path. Anat. 301: 62, 1938.

The author records 26 cases of aneurysm of the arteries at the base of the brain encountered during the past decade. Fourteen of these exhibited congenital defects of the circle of Willis, but, in four of these fourteen, recurrent endocarditis was also found and had, therefore, to be considered as a possible cause of the aneurysm. It is interesting to note that four patients suffered, presumably, from arterial hypertension. He concludes naturally that anomalies of the circle of Willis are important in the development of aneurysm in the neighborhood.

STEELE.

De Takáts, Geza: Vascular Accidents of the Extremities. J. A. M. A. 110: 1075, 1938.

The author summarizes, at some length, the clinical picture, abnormal physiology, and treatment of arterial hemorrhage, arterial embolism, arterial thrombosis, venous hemorrhage, and venous thrombosis. Though surgical measures are frequently essential to proper treatment, of no less value is painstaking care by a physician who is capable of accurately diagnosing, localizing, and treating the special vascular emergency.

Though it is impossible in a summary to include most of the sharply drawn decisions for treatment of one or another such emergency, several of the more important, less well known ones will be mentioned: (1) Ambulatory treatment of thrombophlebitis is preferred to that of prolonged bed rest with one important exception—thrombosis of the perforating veins of the muscles of the calf of the leg. There is a high incidence of pulmonary embolism if prolonged bed rest is not enforced and venous ligation is not performed. (2) Sudden vascular occlusion, by any process, usually is quickly followed by spasm in nearby vessels. This spasm, untreated, is frequently the cause of loss of limb, and yet the spastic vessels are successfully subject to treatment by various vasodilating procedures such as mild heat, intravenous papaverine, or intravenous sodium nitrite. (3) Limbs endangered by arterial embolism have frequently been saved by such procedures, but if signs of inadequate circulation persist for more than an hour or two, embolectomy should usually be performed. Statistics show clearly its value in selected cases. Since the upper extremities are much less subject to gangrene by major arterial occlusion than are the lower extremities, embolectomy in the upper extremities is rarely performed.

MONTGOMERY.

Blasingame, F. J. L.: Thrombotic Occlusion of Superior Vena Cava and Its Tributaries, Associated With Established Collateral Circulation. Arch. Path. 25: 361, 1938.

No history was available. The pathologic finding was that of chronic, complete thrombosis of the superior vena cava, with complete occlusion of both innominate veins. There were some thrombi in the internal jugular and axillary veins, but not sufficient to prevent collateral circulation via the external jugular, transverse cervical, transverse scapular, and azygos veins, to the inferior vena cava. The veins of the upper extremities were larger than usual. A detailed description of the collateral pathways is given.

MONTGOMERY.

Springorum, P. W.: The Importance of the Cutaneous Vessels for the Systemic Circulation. Klin. Wchnschr. 17: 11, 1938.

Simultaneous records of arterial pressure (intra-arterial cannula) and blood flow to and from a given area of skin (one Rein's Stromuhr on the artery to, and a second on the vein from, the area) show that the skin is a not inconsiderable depot for blood. The animals studied were dogs. When histamine is injected, blood is detained in the skin, and, when veritol or adrenalin is injected, blood is released.

A second experiment illustrates the importance of the skin as a blood depot under the influence of heat. If the arterial pressure, cutaneous and muscular blood flows are measured simultaneously, it becomes clear that, when the skin is exposed to a heat lamp, the blood flow through the skin may increase threefold to sixfold and at the expense of flow through the muscles. If the animal has first been bled, so that he is more sensitive to loss of blood into the skin, warming the skin can induce sufficient fall in arterial pressure to cause collapse. He suggests that caution is, therefore, necessary in application of heat to the skin of individuals who are, for any reason on the verge of collapse.

STEELE.

Altscshule, Mark D., and Gilligan, D. Rourke: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man: II. The Dynamics of the Circulation. J. Clin. Investigation 17: 401, 1938.

The effects of the intravenous injection of isotonic and of slightly hypertonic crystalloid solutions on the venous pressure, pulse rate, arterial pressure, cardiac output, velocity of blood flow, respiratory dynamics, electrocardiogram, and blood volume of normal man have been studied.

When 500 to 1500 c.c. of physiologic saline, 5 per cent glucose, or 5 per cent glucose in physiologic saline solutions, were injected at rates of less than 20 c.c. per minute, very slight changes were observed in the cardiovascular functions studied; the blood volume was usually considerably increased.

When these volumes of fluid were injected at more rapid rates considerable increases in venous pressure, cardiac output, velocity of blood flow, and in blood volume were usually observed; increases in pulse rate, pulse pressure, and in the P-wave of the electrocardiogram were observed in some instances.

The greater venous pressure increases occurred in subjects who received fluids in the larger volumes and at the more rapid rates. The venous pressure invariably returned to the control level within ten to twenty-five minutes after the end of fluid administration.

Significant increases in cardiac output occurred in patients in whom the intravenous injection of fluids resulted in rises in venous pressure.

When fluids were injected in larger volume and at more rapid rates, the increase in velocity of blood flow was considerably less than that expected from changes in the cardiac output. In some instances the increase in velocity of blood flow was greater after the injection of 500 c.c. of fluid than after 1000 or 1500 c.c. These findings are interpreted as indicating an increase in pulmonary blood volume during injection. Dyspnea did not occur, and changes in respiratory dynamics were not observed.

The fact that rises in venous pressure did not persist, or even did not occur, in spite of increased blood volume, together with the observation of increasing diffuse flush of the skin, points to a progressive peripheral vasodilatation during the course of injection of fluids. Additional evidence in this regard is the tendency toward increased pulse pressure observed in some subjects.

The clinical implications of these findings are discussed.

AUTHOR.

Veal, James Ross: Factors in the Mortality Rate of Arteriosclerotic Gangrene: A Comparative Study of 214 Cases of Surgical Intervention. J. A. M. A. 110: 785, 1938.

Diabetic gangrene is not included. A series of 110 cases of amputation for arteriosclerotic gangrene performed in the New Orleans Charity Hospital in the five-year period ending in 1933 resulted in a mortality of 39.1 per cent. During the next three-and-one-half-year period, a series of 104 such cases had a mortality of 28.8 per cent. An explanation for the lowered mortality seems to rest in more careful preoperative and postoperative care: prompt amputation, free use of fluids, infusions of dextrose, frequent moving of the patient, early postoperative removal from bed to chair, keeping the amputation stump in a dependent rather than an elevated position, and the use of a heat cradle at not more than 100° F. In both series the commonest cause of death was pneumonia, the incidence of which was lowered a little in the recent series. Shock was the second commonest cause of death in the first series but the sixth cause in the recent series. Cardiac failure (congestive failure and coronary thrombosis) was the fourth cause in the first series but the second cause in the recent series. The incidence of cardiac failure in the recent series was nearly double that in the first series.

Three factors pointing to poor prognosis are extensive gangrene, evidences of arteriosclerosis in vital organs, and preoperative fever. Gas gangrene was an infrequent complication. Primary healing occurred in only 35 of the 54 patients surviving amputation. Recurrent gangrene carried a very high mortality. Some roentgenologic evidence is presented with the theory that emboli from the amputation stump are a cause of postamputation pneumonia. It is suggested that infusions of dextrose rather than of saline solution may help prevent cardiac failure associated with acute pulmonary edema.

MONTGOMERY.

Kandel, E. V.: Fever of Undetermined Origin in a Patient With Traumatic Brachial Aneurysm Cured by Excision. J. A. M. A. 110: 891, 1938.

The patient had pain for four years in the site of what proved to be the aneurysm. He had chills, fever, nausea, and vomiting for the month and a half immediately preceding excision of the aneurysm. Symptoms ceased when the aneurysm was excised. Culture of its tissue yielded a diphtheroid bacillus. Microscopic examination of the tissue showed only remnants of chronic inflammation. No blood cultures were reported.

MONTGOMERY.

Bazett, H. C.: Some Principles Involved in Treatment by Heat and Cold. Med. Record 147: 301, 1938.

Various workers have given statistics for the seasonal distribution of initial attacks of symptoms of angina pectoris, coronary occlusion, myocarditis, endocarditis, thrombosis, embolism, cerebral hemorrhage and aneurysm. Data of this kind collected by Dr. L. B. La Place, for the author, show that the incidence is greatest at the times that the physiologic strain would be expected to be greatest—namely, at the times of sudden climatic changes, early summer, and particularly at the onset of cold in the autumn. The highest peaks are in November and February; the minimum, in August. Vasoconstriction imposed by a sudden increase in cold obviously puts an immense strain on the circulatory system. Possibly this strain is partly dependent on the presence of the large blood volume of summer. Patients of such a type should be carefully guarded from sudden exposure to cold after acclimatization to heat treatment. If the theory is sound, then at the completion of a series of heat treatments during which the patient has also been kept under warm conditions, bleeding before returning him to a cold climate might be sound prophylaxis in selected cases.

MONTGOMERY.

Brown, James Barrett: The Interstitial Radiation Treatment of Hemangiomata. Am. J. Surg. 39: 452, 1938.

All hemangiomas that exhibit any growth tendency should be treated early. Arterial hemangiomas may present trying therapeutic problems when both their presence and their treatment threaten the patient with deformity. Cautery destruction or surgical excision should be used in areas where the scar does not show. Radiation, properly given, does not scar. Because most hemangiomas have elements some distance from the surface, interstitial rather than surface radiation is advisable. The interstitial implantation of gold radon seeds in the author's experience is the most valuable single method of therapy where surgical excision or surface radium is not applicable. Usually within a week's time there is a definite decrease in the blood flow through the tumor. The reaction reaches its peak within two to three weeks, and shortly after this the most speedy recession of the growth is noted. Progressive improvement may follow for six months following a single treatment. Even large involvements may be stopped with a single treatment, where it has been recognized that months or even years might be necessary with surface radiation.

MONTGOMERY.

Krock, Fred H.: A Simplified Apparatus for Pressure-Suction Therapy of Obliterative Arterial Disease of the Extremities. South. M. J. 31: 294, 1938.

The remarkable development of collateral circulation occurring in some cases of organic obliterative arterial disease of the extremities following the use of pressure-suction therapy is so striking that this form of treatment has become almost standard in the past four years. The apparatus has, however, been expensive; ranging in price from $350 to $1000. A simplified apparatus, which has long life and an even wider range of pressures, has been designed. The entire equipment with two boots and two complete sets of cuffs can be constructed for slightly less than $100. No manufacturer is named.

MONTGOMERY.

Book Reviews

SUBACUTE AND CHRONIC PERICARDIAL AND MYOCARDIAL LESIONS DUE TO TRAUMATIC INJURIES. A Clinical Study. By Erik Warburg, M.D., With a Short Biography of Oluff Borch by Torben Geill, M.D., Copenhagen, 1938, Levin & Munksgaard; London, 1938, Oxford University Press.

This book of 147 pages deals with nonpenetrating injuries of the heart and pericardium in patients who lived for a period of six days or longer. Cases of rupture of the valves or chronic valvular disease were excluded. The compilation of 197 cases occupies sixty pages, and the analysis of this material occupies twenty pages. Some of the cases are questionable examples of cardiac trauma. Even in the group of sixty cases in which post-mortem examinations were carried out there were nine cases that the author refused to accept as examples of cardiac trauma. The fifty-one satisfactory autopsy cases were analyzed according to period of survival, age of patient, type of lesion, onset of symptoms, and type of accident. A group of thirty-one so-called pericardial lesions was given. In twelve cases there were transitory alterations in the electrocardiogram. In a group of ninety cases the diagnosis was based upon the course followed after the accident. A description of the clinical picture took up eight pages, Borch's biography eight pages, and references and index seventeen pages.

The book contains much information on an important subject. Contusions of the heart are common injuries. Treatment is discussed in one-third of one page. The use of quinidine is not mentioned. Surgical operation in cases of rupture is not advocated. Only one patient in the entire group was operated upon, and this patient was saved by the timely evacuation of blood from the pericardial cavity; but Warburg, unfortunately, sees no possibility for surgical development in this field.

Borch is given a prominent place in the book because he described what Warburg accepts as the first case of nonpenetrating cardiac injury in 1676, whereas Blanchard's case was not reported until 1688. Perhaps the reader will be interested in these obscure and hoary documents but I believe that these early cases are somewhat questionable examples of cardiac trauma and are of little practical value.

The book is valuable, but the author is not highly successful in giving to his reader a vivid picture of this important subject with all of its variable clinical manifestations, legal aspects, prognosis, and treatment.

CLAUDE S. BECK.

ELEMENTI DI CARDIOLOGIA ED ELETTROCARDIOGRAFIA, Vol. I—Parte Generale. By Dr. Stefano Biondo. Palermo, 1937, L. Salpietra, Editore.

Stefano Biondo's *Elementi di Cardiologia ed Elettrocardiografia* is essentially an elementary thesis of 238 pages for students who may wish to acquaint themselves with some of our present knowledge of electrocardiography. It is not concerned with details of anatomy, physiology, or pathology but deals somewhat with pharmacology and instrumental technique.

The book is divided into twelve chapters, the first three of which deal with history taking, symptoms, and examination of the patient. A short chapter deals with the sphygmograph, x-ray, and electrocardiograph. About 100 pages on normal and

pathologic electrocardiograms follow. A chapter is devoted to myocardial insufficiency and its various phases and treatment. In a few pages the author discusses diagnosis, prognosis, and the use of digitalis and drugs having a similar action. A short chapter is devoted to the prevention of heart disease.

The book contains a good bibliography but no detailed study of cases such as one would like to see in a thesis of this sort.

GERARDO M. BALBONI.

Erratum

In the article, "Sclerosing of Varicose Veins by Ligation and One Massive Injection of Sodium Ricinoleate (Soricin)," by Samuel H. Sedwitz, M.D., and Myron H. Steinberg, M.D., which appeared in the June issue of the JOURNAL, the test referred to on page 674, lines 2 and 20, as the Buerger test should have been called the Samuels modification of the Buerger test; the modification is the active flexion and extension of the foot while it is elevated.

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Original Communications

INFARCTION OF THE LATERAL WALL OF THE LEFT VENTRICLE: ELECTROCARDIOGRAPHIC CHARACTERISTICS*†

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PHILADELPHIA, PA.

PATHOLOGIC studies[2] have shown that, in general, there are three main sites of cardiac infarction: (1) the "anterior apical," (2) the "posterior basal," and (3) the "midventricular," located in the left posterolateral wall of the heart. The electrocardiographic signs of the first two have been established.[3] The present paper has to do with the recognition of the third, the less common, type of cardiac infarction.

Our observations indicate that: (1) Lateral infarction, like the other two, seems to have its own electrocardiographic pattern. (2) This pattern can be mimicked rather closely, in certain cases, by digitalis action. (3) The electrocardiographic features of the acute lesion may subside very rapidly; the tracing during the process of healing may be indistinguishable from that of certain hypertensive patients without cardiac infarction. (4) After healing of the infarction, all the changes produced by it may disappear from the tracing. (5) This group of cases has a very high incidence of auricular fibrillation. (6) Without knowledge of these facts it is possible to make the dangerous mistake of overlooking the presence of this type of acute cardiac infarction.

The electrocardiographic pattern of acute "lateral" or "midventricular" infarction is illustrated by Case 1, Fig. 1*B*. The main features are (1) a depression of the RS-T interval in Lead IV, (2) a depression of the RS-T interval in Leads I and II (commonly, though not universally present), and (3) an absence of the signs of posterior infarction in

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†All tracings in this paper are shown as if they were taken by the technique recommended by the Committee of the American Heart Association for the Standardization of Precordial Leads,[1] and are described in the terminology suggested by it.

Received for publication May 21, 1938.

Lead III. In the typical case the RS-T interval depression in precordial leads is more marked when the anterior electrode is placed at or to the left of the apex, than when it is put nearer the sternum (Fig. 2, Cases 2, 3, and 19). Lead III shows left axis deviation in 12 of the 20 cases. However, in five cases (1, 3, 7, 8, and 10) in which former tracings are available for comparison the QRS complex in Lead III is the same before and after the attack. Consequently, left axis deviation cannot be considered an integral part of the electrocardiographic pattern of lateral infarction. One patient with a significant Q_3 is included in this series (Case 10)* because this wave was present prior to the attack in which lateral infarction is thought to have occurred. The QRS complex, not only in Lead III, but in all leads, seems to be singularly unaffected by

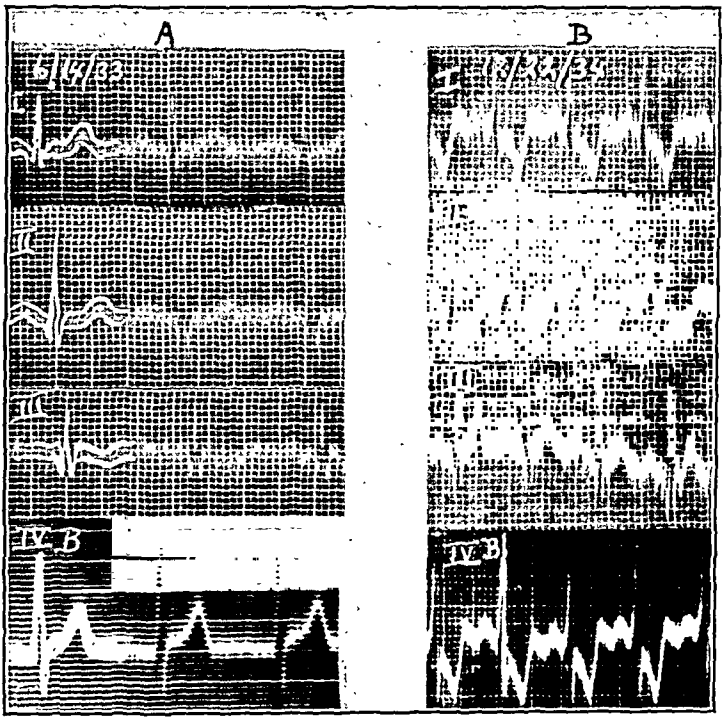

Fig. 1.—Electrocardiograms in Case 1.

In this case and in a number of others, the precordial leads were originally taken with our old technique.[3] However, in order to avoid confusion, they have been rephotographed and printed with the film reversed. Thus, in all figures in this paper, the precordial leads appear as though they had been taken according to the recent recommendations of the Committee for Standardization of Precordial Leads of the American Heart Association.[1]

A, normal tracing taken June 14, 1933, eighteen months before the attack.

B, tracing taken Dec. 22, 1934, nine hours after the attack began, showing evidences of acute lateral infarction. The RS-T interval is depressed in Leads I, II, and IV. Lead III is within normal limits, but shows a marked change in the T-wave since June 14, 1933. The QRS complex has not been changed by the infarction. The patient died ten hours after this electrocardiogram was taken. Necropsy showed a recent infarct in the left lateral wall of the heart.

this type of infarction. The only definite change we have seen was in Case 7 (Fig. 4). In the tracing of this patient the S-wave in Lead IV-B was definitely smaller after the attack than before it.

*Fig. 1 of an earlier paper[4] shows the electrocardiogram in a similar case. A significant Q_3 was present before as well as after an attack which may have been caused by lateral infarction.

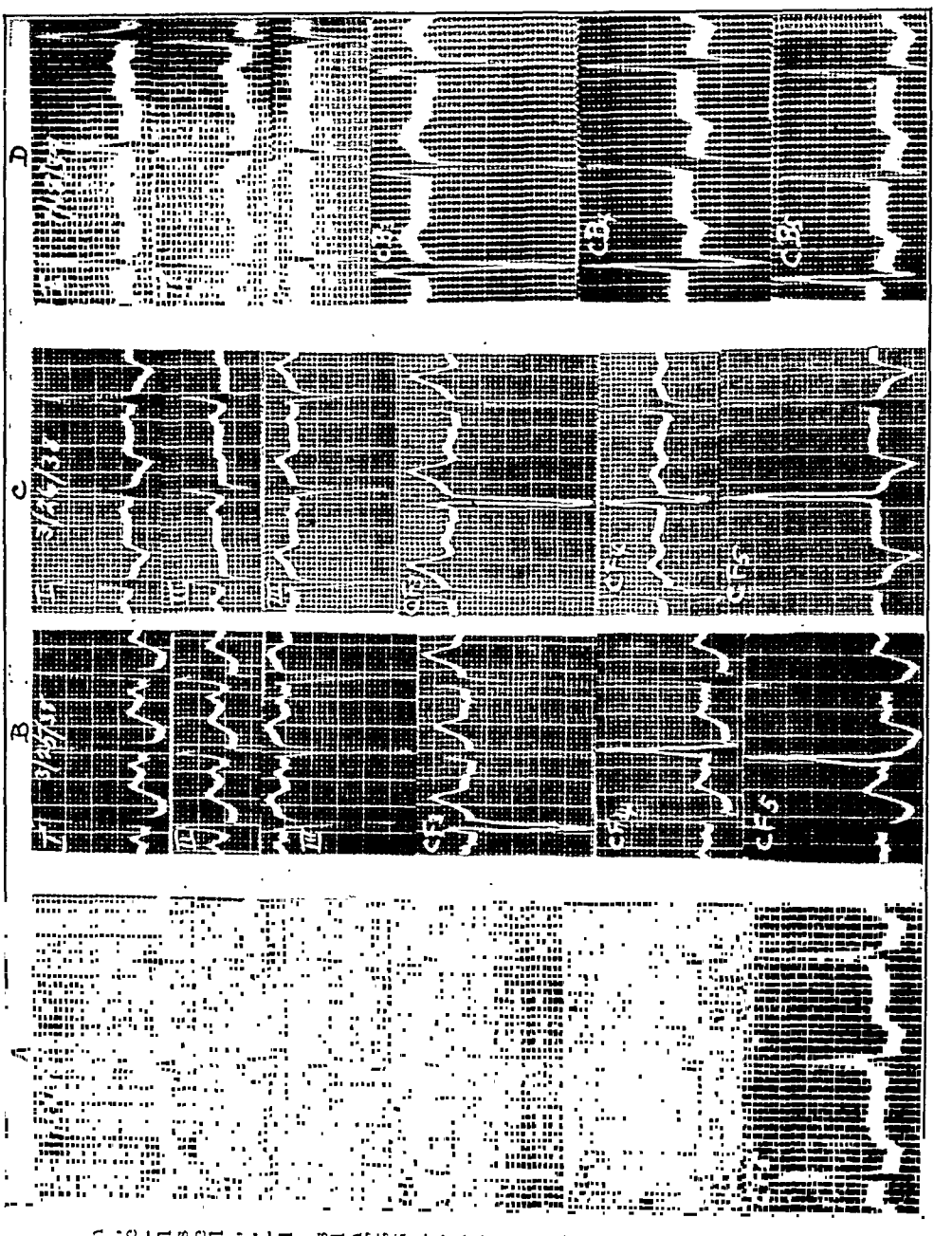

Fig. 2.—*A*, electrocardiogram in Case 2, taken Jan. 22, 1938, seven hours after the onset. The RS-T interval is slightly depressed in Leads I and II. Lead III is normal except for left axis deviation. In precordial leads the depression of the RS-T interval is seen in leads CF_4 and CF_5, but not in CF_3. Necropsy on Jan. 27, 1938, showed recent myocardial damage in the left lateral wall of the heart.

B and *C*, electrocardiograms in Case 19, taken March 25 and 26, 1938. *B*, the tracing taken four hours after the onset of pain, shows the typical pattern of acute lateral infarction. The RS-T interval in Leads I and II is depressed. Lead III is normal except for left axis deviation. In precordial leads the depression of the RS-T interval is marked in CF_4 and CF_5, but CF_3 falls to show it. *C*, a tracing taken twenty-four hours after the attack, shows a complete disappearance of the signs by which the healing infarction could be recognized. The electrocardiogram might well be that of a patient with hypertension without cardiac infarction.

D, electrocardiogram in Case 3, taken Jan. 18, 1937, four days after the last attack of pain. The RS-T interval depressions in Leads I and II are subsiding. Left axis deviation is present. In precordial leads the RS-T interval depression is present in CB_5 and CB_6 but absent from CB_5.

An electrocardiogram almost exactly like that in Case 1 was obtained from a patient during a brief attack of effort angina (Case 21, Fig. 5). Similar evanescent electrocardiographic changes are reported by Jervel[5a] and by Levy, Barach and Bruenn.[5b] It is clear, therefore, that the electrocardiographic pattern of lateral infarction, since it lacks changes in the QRS complex, can be produced by temporary ischemia as readily as by the more permanent circulatory interruption of coronary thrombosis. Furthermore, after the anginal attack the tracing may return completely to normal (Fig. 5*C*).

The electrocardiographic pattern of lateral infarction might be confused with that of posterior infarction on the one hand, or with that of pulmonary embolism[6] on the other, because the precordial leads of all

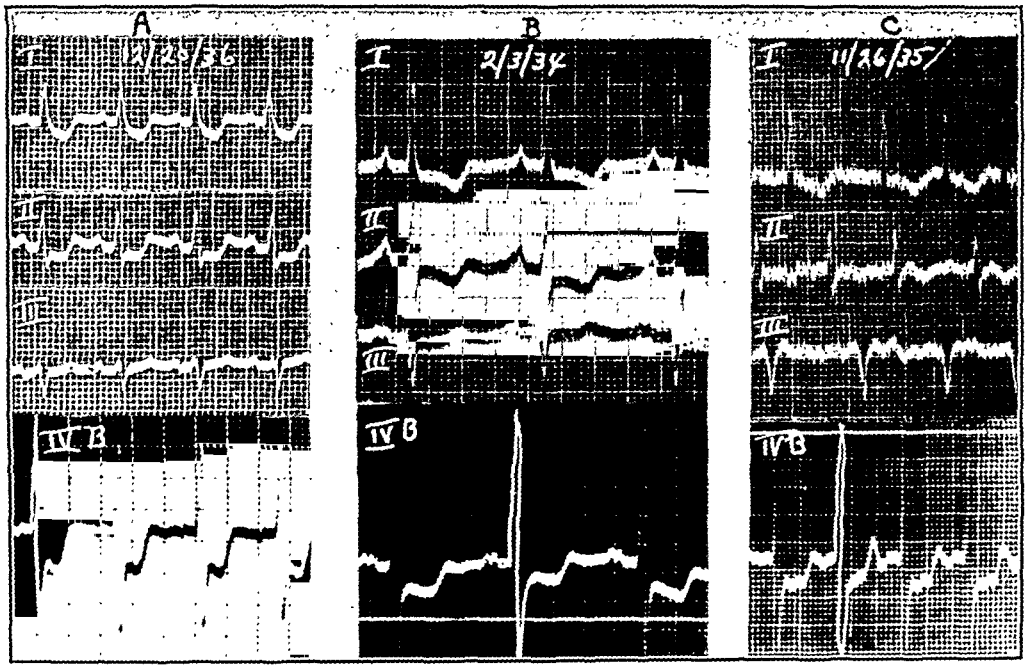

Fig. 3.—*A*, electrocardiogram in Case 4, taken Dec. 20, 1936, twelve hours after the onset. The typical signs of acute lateral infarction are apparent. The RS-T interval in Leads I, II and IV-B is markedly depressed. Lead III is normal except for slight left axis deviation.

B, electrocardiogram in Case 11, taken Feb. 3, 1934, two days after a severe attack of cardiac pain. The signs of recent lateral infarction are present. The RS-T interval in Leads I, II and IV-B is markedly depressed. Slight left axis deviation is present.

C, electrocardiogram in Case 5, taken Nov. 26, 1935, thirty-six hours after the attack. It shows auricular fibrillation, inversion of T_1 and T_2, left axis deviation, and a marked depression of the RS-T interval in Lead IV-B.

three may be similar. However, posterior infarction can usually be differentiated because it has a significant Q_3 and an elevation of the RS-T interval in Leads II and III. Moreover, pulmonary embolism differs in that T_1 is usually upright and T_3 usually inverted.

The evidence that the lesion is lateral or posterolateral in these cases may be summed up as follows:

1. One typical, uncomplicated, autopsy case is available (Case 1). In a second (Case 2) there was no gross infarction at necropsy; but the history of an attack of pain, combined with the finding of recent

thrombosis of a branch of the left circumflex artery and definite histologic changes in the lateral wall of the heart, makes this case a strong link in the chain of evidence. In the third necropsy case (Case 10) there was an old circumflex artery occlusion, but clinicopathologic correlation here is uncertain because of the fourteen-month interval between the attack and the necropsy.

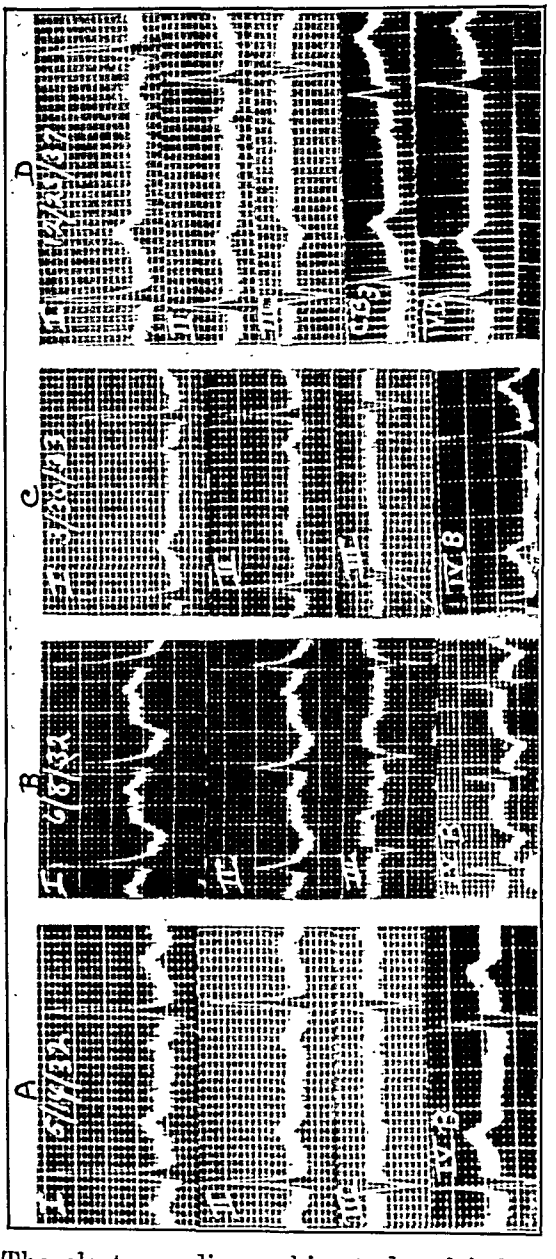

FIG. 4.—Electrocardiograms in Case 7.

A, tracing taken May 14, 1932, three weeks before the attack. It is normal except for left axis deviation.

B, tracing taken June 8, 1932, two hours after the onset of the attack. The RS-T interval is depressed in Leads I, II, and IV. Lead III shows slight left axis deviation, and a slight RS-T interval elevation.

C, tracing taken March 30, 1933, fifteen months after the attack. It is very much like the electrocardiogram of May 14, 1932, prior to the cardiac infarction, except that the S-wave in Lead IV-B has disappeared. This did not take place immediately after the attack, but at some time between June 20, 1932 and March 30, 1933.

D, electrocardiogram taken Dec. 23, 1937, showing that the S-wave in Lead IV-B is still absent. In a lead taken with the precordial electrode nearer the sternum (CB_5), the S-wave is present but much smaller than it was in Lead IV-B before the attack. (Lead CB_5 is ordinarily expected to have a larger S-wave than Lead IV-B.)

2. The electrocardiographic study of infarction in other parts of the heart indicates that myocardial ischemia in a certain location tends to produce a characteristic electrocardiographic pattern. Thus, it is reasonable to suppose that the seventeen cases without necropsy were instances of lateral infarction.

3. This group of cases corresponds in relative size with the group of cases of "midventricular" infarction described pathologically by Barnes and Ball,[2] in that it is smaller than the groups of either anterior or posterior infarction.

4. Even before Case 1 appeared, the electrocardiographic characteristics shown by these patients led us to believe that the lesion was located posterolaterally[4, 7] away from the septum. This belief was based on the fact that (a) Lead IV showed a depression of the RS-T interval (i.e., a posterior rather than an anterior localizing sign), (b) the Q_3 (supposed to be due to a lesion in or near the posterior basal portion of the interventricular septum) did not appear, and (c) the RS-T interval elevation in Lead III, so characteristic of typical posterior infarction, was absent.

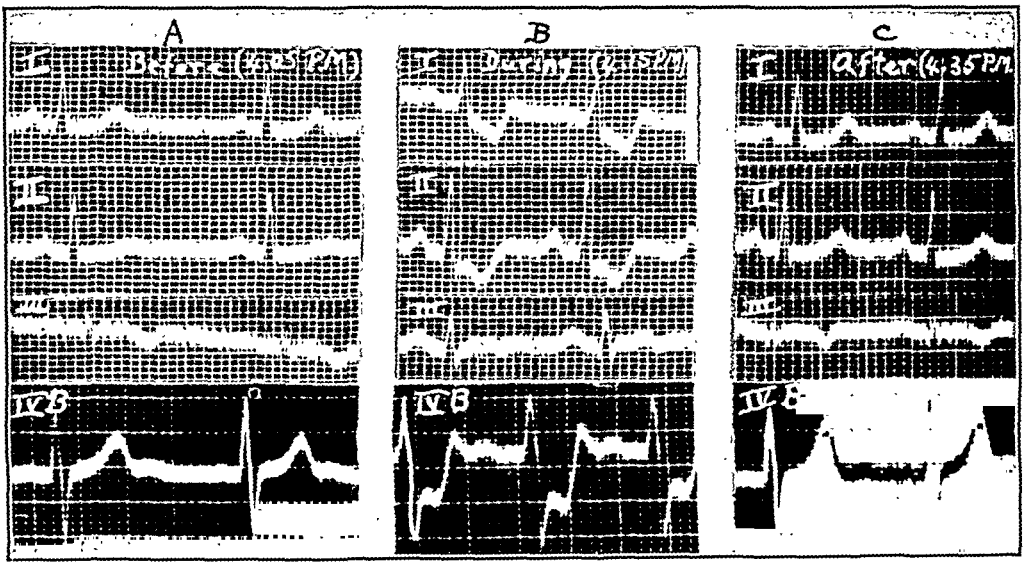

Fig. 5.—Tracings in Case 21, taken May 19, 1934, which show that the typical electrocardiographic pattern of acute lateral infarction can appear temporarily during an attack of effort angina.

A, taken at 4:05 P.M., before exercise, showing no definite abnormalities. The subject then induced lower sternal discomfort of moderate degree by stepping up on a chair twenty-five times, and then swinging his arms for a brief period.

B, taken at 4:15 P.M., during the height of his discomfort. The patient classified this attack as of only moderate severity, compared with others he had experienced. The typical pattern of acute lateral infarction has appeared. The RS-T interval in Leads I, II, and IV has become markedly depressed. The deviation in RS-T IV is the largest we have ever seen during an attack of effort angina.

C, taken at 4:35 P.M., after the discomfort had subsided. The tracing has returned to normal, and looks much like it did before the attack. The evidence suggests that this patient had ischemia of the left lateral wall of the heart during this attack of effort angina.

Final acceptance of the fact that this electrocardiographic pattern is caused by lateral infarction should probably await the report of other necropsy cases, uncomplicated by digitalis medication or by multiple myocardial lesions. However, all available evidence would seem to favor this point of view.

Atypical Cases.—Midventricular or lateral infarction usually results from occlusion of the circumflex branch of the left coronary artery.[2]

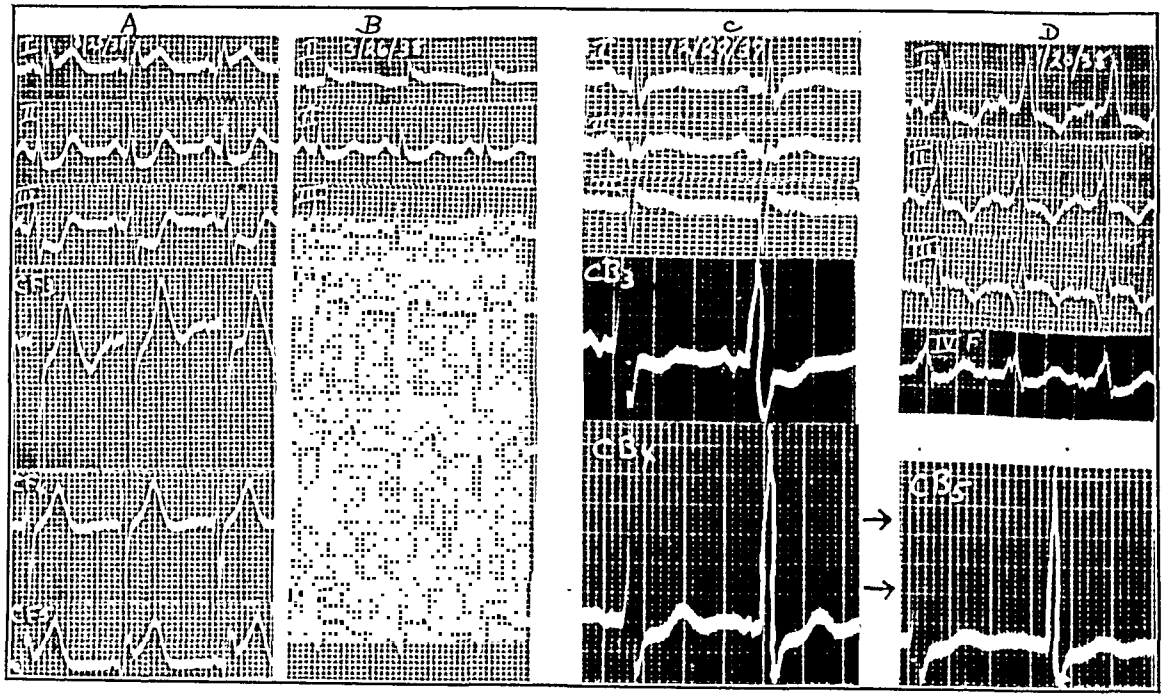

Fig. 6.—Atypical cases.

A and *B*. Electrocardiograms in Case 22.

A, tracing taken March 25, 1938, on the day of onset. The limb leads suggest anterior infarction. The precordial leads seem superficially contradictory. CF_3 shows an RS-T interval depression, suggesting lateral or posterior infarction; CF_1 is normal; CF_5 shows a Q-wave and an RS-T interval elevation. Anterolateral infarction was suggested ante mortem as an explanation for this electrocardiogram.

This tracing illustrates the marked differences which may occur in certain cases between Leads CF_3, CF_1 and CF_5. All three may be worth taking in certain patients with coronary disease.

B, tracing taken in Case 22, March 26, 1938, showing the typical pattern of acute anterior infarction in limb leads. The precordial leads have changed markedly, suggesting an enlargement of the lesion in the anterior wall of the left ventricle. Lead CF_5 shows the most marked RS-T interval elevation of any precordial lead. Necropsy March 28, 1937, showed old occlusion of the left anterior descending artery, and recent occlusion of the left circumflex artery with extensive infarction of the anterior and lateral walls of the left ventricle.

C, electrocardiogram in Case 24 taken Dec. 29, 1937. Leads II and III show RS-T interval elevation. Lead III shows a Q-wave. Precordial leads show a depression of the RS-T interval, which in this case is as marked in CF_3 as in CF_1 and CF_5. Necropsy Jan. 3, 1938, revealed old occlusion of left anterior descending and right coronary arteries, with recent occlusion of the left circumflex. There was an extensive infarct involving the posterior and lateral walls of the left ventricle.

D, electrocardiogram in Case 23, taken Jan. 20, 1938, showing evidences of recent lateral infarction (i.e., an RS-T interval depression in Leads I, II, and IV) combined with the signs of fresh posterior infarction (i.e., a significant Q-wave and an RS-T interval elevation in Lead III). Necropsy Jan. 24, 1938, showed a small patent right coronary artery, an old occlusion of the left anterior descending artery, and a recent occlusion of the large left circumflex. There was extensive infarction of the posterior and lateral walls of the left ventricle, and of the posterior part of the interventricular septum.

However, in a heart with an unusually large left circumflex or with neighboring arteries congenitally small or obstructed by disease, occlusion of this vessel may give rise to a more extensive lesion which may invade the anterior or the posterior wall of the left ventricle. Thus complex electrocardiographic patterns may be produced. Four such cases have been seen by us, each with necropsy (Cases 22 to 25, inclusive). Case 22 is an example of circumflex occlusion which produced infarction extending to the anterior wall because of former occlusion of the left anterior descending artery. The anterolateral location of the lesion was suggested by the tracing obtained on March 25, 1938, (Fig. 6*A*).* The other three are examples of circumflex occlusion with extension of infarction into the posterior wall of the left ventricle. In all three the circumflex artery was unusually† large and the other coronary arteries were either unusually small (Case 25), or obstructed as a result of previous disease (Cases 23 and 24). The electrocardiogram in Case 23 (Fig. 6*D*) is fairly typical of lateral infarction except that Lead III has the characteristics of posterior infarction. In Case 24 (Fig. 6*C*) the chest leads suggest lateral or posterior infarction, but the RS-T interval is elevated in Leads II and III, and Q_3 is present. In Case 25 there is a tendency to right axis deviation (the patient had mitral stenosis); the T-waves in the limb leads are normal; a definite RS-T interval depression is present in Lead IV-B.

In the study of our cases of lateral infarction, three peculiarities have been encountered which have made the diagnosis difficult:

I. There is a high incidence of auricular fibrillation. If we include the four patients with infarction extending beyond the "midventricular" region, the group totals 24. Ten of these showed auricular fibrillation at some time during their course. One (Case 9) had a 48-hour paroxysm following prostatectomy, 9 weeks after his coronary occlusion. Two patients (Cases 6 and 8) probably had fibrillation before, as well as after, the attacks we studied. In a fourth (Case 18) the time of onset of the fibrillation is not definitely known. However, since the arrhythmia ceased a few days after admission, it was probably a paroxysm accompanying the coronary attack. In a fifth (Case 25) mitral stenosis was present and may have predisposed the patient to the occurrence of auricular fibrillation. The sixth patient (Case 10) had a good many paroxysms of auricular fibrillation, often accompanied by cardiac pain. On April 24, 1933, when we suspect that a lateral infarction occurred,

*For some time it has been obvious that in certain cases of coronary occlusion a single chest lead is inadequate to elicit all available diagnostic information. Case 22, Fig. 6*A*, is an example of the differences which sometimes exist between tracings taken with the anterior electrode at three different points on the precordium. On account of the findings in cases of this sort, we are, at present, using three precordial leads, CF_3, CF_4 and CF_5, in all patients suspected of having coronary disease.

†"Unusually" may be too strong a term. Gross[5] has shown that in about one of every ten individuals the circumflex branch of the left coronary artery is a large vessel which continues on to form the posterior descending artery, and supplies the entire posterior surface of the left ventricle. In hearts in which this anatomical situation exists (Cases 23 and 25), the "atypical" vascular pattern may regularly produce an "atypical" electrocardiographic pattern when the left circumflex artery is occluded.

he had an especially long paroxysm. The four other patients (Cases 2, 22, 5, and 17) developed fibrillation at the time of their cardiac infarction. In the first two the rhythm returned to normal, and in the last

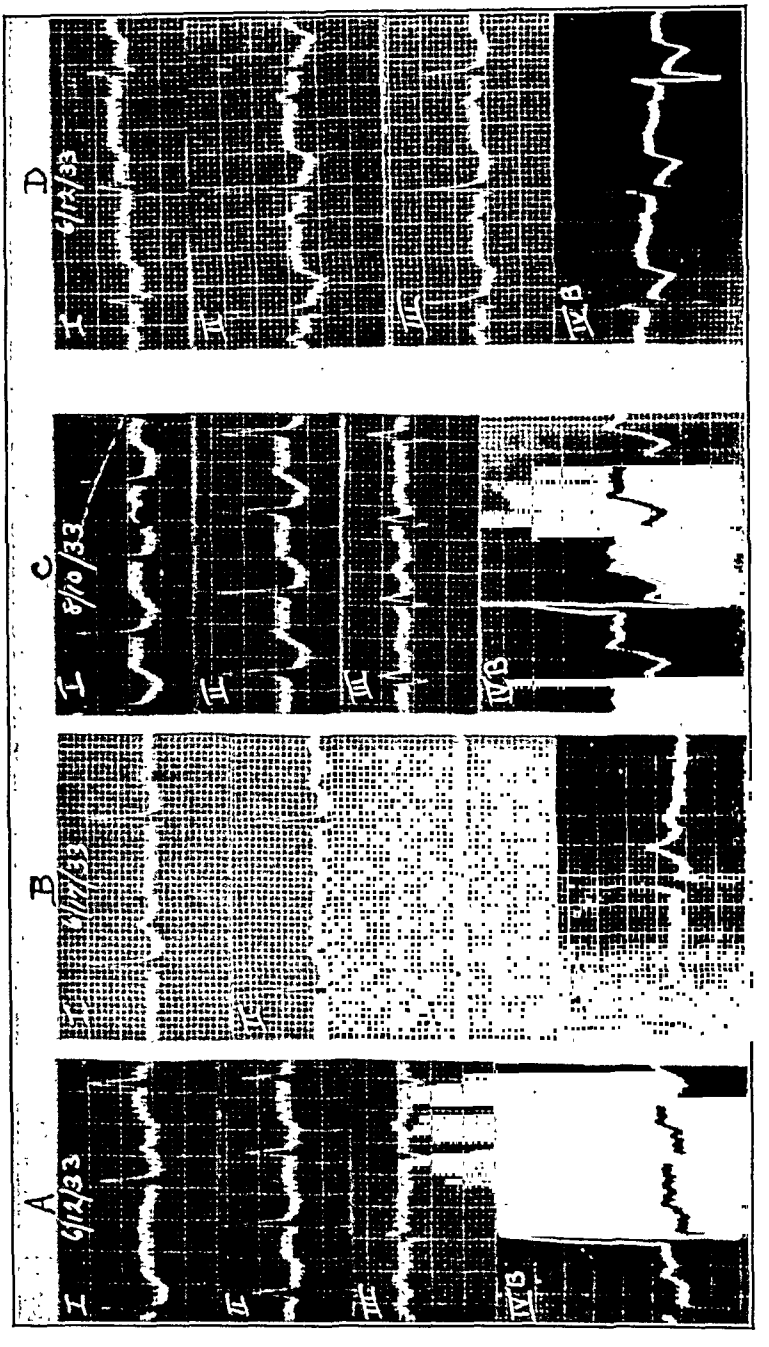

FIG. 7.—Digitalis effects.
A, *B*, and *C* are electrocardiograms in Case 17. They all show auricular fibrillation, which began at the time of the attack, June 8, 1933. *A* is the tracing taken June 12, 1933. It has a suggestion of a depression of the RS-T interval in Leads I and II, and a definite depression of this interval in Lead IV-B. *B* is the tracing taken June 17, 1933, which shows a return of the RS-T interval deviations towards the isoelectric line. *C* is the tracing taken Aug. 10, 1933, when clinical evidences suggested that the infarct had healed. The patient was fully digitalized at this time. The typical electrocardiographic pattern of acute lateral infarction is present.
D is the tracing of a man of 50 years without demonstrable heart disease. On May 24, 1933, his electrocardiogram was normal. Beginning May 25, 1933, he received 6 c.c. of the tincture of digitalis daily. On June 12, 1933, the electrocardiogram shown in *D* was taken. It has a depression of the RS-T interval in all four leads, the usual result of digitalis action when the electrical axis is normal.
When digitalis was stopped, the tracing returned to its original configuration.

two the arrhythmia persisted. Thus, the evidence suggests an etiologic relationship between the attack of pain and the onset of auricular fibrillation in at least four cases, and probably in seven. In the remaining three cases, it is not impossible that the arrhythmia was related to the coronary lesion.

As a background for comparison, the records of 124 unselected cases of coronary occlusion were reviewed. Only six patients had auricular fibrillation. Dividing these cases into groups shows the following: In 64 cases of anterior infarction, there were 5 with auricular fibrillation, all with relatively brief paroxysms. One of these patients also had an attack of auricular flutter. Among 10 patients suspected of having anterior and posterior infarction,[9] one had a short paroxysm of fibrillation. In the remaining 50 cases, 37 with posterior infarction, 11 with huge T-waves in chest leads,[10] and two with infarction of doubtful location, there was no instance of auricular fibrillation. Thus, no matter how the figures of the cases of lateral infarction are interpreted, whether there are 10 of 24, 7 of 24, or only 4 of 24 with a definite relationship between the coronary attack and the arrhythmia, the incidence is higher than that of its nearest rival (1 in 10), and much higher than that of the entire coronary group (1 in 20).

The cause for this high incidence of auricular fibrillation in lateral infarction is not known. It may be that the auricular muscle is deprived of a necessary part of its blood supply by circumflex occlusion. Digitalis could not have been an important factor since 7 of the 10 patients received none of this drug prior to the onset of arrhythmia.

II. Digitalis administration may produce an electrocardiographic pattern similar to that of lateral infarction.[11] Because of the high incidence of auricular fibrillation, this factor comes into play with a frequency unparalleled in other types of coronary occlusion. In patients with a normal electrical axis, with the main deflection of QRS in Lead III directed upward, digitalis depresses the RS-T interval in all four leads (Fig. 7*D*), and gives a little diagnostic difficulty. In patients with left axis deviation, digitalis depresses the RS-T interval in Leads I, II, and IV, and elevates it in Lead III. Thus, with mild degrees of left axis deviation the effect of this drug might closely mimic the lateral occlusion pattern. In only one type of case, however, have we seen digitalis reproduce exactly the picture of acute lateral infarction, i.e., in a patient with a healed lateral infarct. This phenomenon has been observed in other types of coronary occlusion.[12] The patient in Case 17 (Fig. 7*C*) is probably an example. His attack occurred June 8, 1933. RS-T interval deviations, which were present June 12 (Fig. 7*A*), began to subside June 17 (Fig. 7*B*). The lesion had probably healed fairly well by Aug. 10, 1933, as far as could be determined on clinical grounds. However, at this time, when the patient was fully digitalized, the tracing shows the most marked RS-T interval deviations with the typical picture of acute lateral infarction (Fig. 7*C*). Other examples of this phenomenon are the electrocardiogram of the patient in Case 16, taken on March 16, 1936, and possibly the tracings in Case 8 (Nov. 23, 1933), Case 13 (Dec. 19, 1932) and Case 15.

This brings up the question whether, in this group of cases, some or all of the electrocardiographic features which we have attributed to lateral infarction might have been due to digitalis. The facts are these: Prior to the taking of the first, or at least the significant electrocardiogram, 5 patients were probably digitalized though free from toxic effects (Cases 6, 8, 9, 13 and 15); 2 had received 12 cat units or less (Cases 7 and 18); 2 had received less than 6 cat units (Cases 2 and 17); 11 had received no digitalis at all. Thus the chances that any but the first five had received enough of the drug to cause the electrocardiographic changes would seem to be meager. Moreover, even in them it is hardly proper to attribute the electrocardiographic features to digitalis because (1) comparatively few patients have marked RS-T interval deviations from digitalis without toxic symptoms, such as nausea and vomiting, or marked asthenia, (2) few digitalized patients show the exact pattern of lateral infarction, and (3) all five of our patients had attacks of pain which suggested coronary occlusion.

Nevertheless, when confronted with an electrocardiogram suggesting recent lateral infarction, especially if left axis deviation is present, one should remember that digitalis can, very nearly, reproduce the pattern. Moreover, in old people with myocardial disease, much less of the drug is required to cause RS-T interval deviations than is necessary in young healthy subjects, and the effects in this older group persist much longer than in young individuals.

III. After RS-T interval deviations disappear the lesion becomes unrecognizable electrocardiographically. In seven patients repeated tracings were taken during the healing of the infarct. After the attack the RS-T interval reached the isoelectric line within the following time intervals: Case 19, 24 hours; Case 7, 2 days; Case 10, 3 days; Case 20, 7 days; Case 3, 13 days; Case 14, 21 days; and Case 11, 28 days; although the typical pattern, by means of which the diagnosis could be readily established, often became indistinct sooner than this. At the end of these periods of time, the electrocardiogram usually showed an inversion of T_1 and T_4, a diphasic T_2 and an upright T_3. When left axis deviation was present (6 of 7 cases), the tracing could not be distinguished from the pattern often seen in patients with hypertension without cardiac infarction.

Nine patients, whose last tracings were free from digitalis effects, were followed electrocardiographically for a month or more, i.e., into the "healed stage." Three different end results were observed. (a) Five retained the hypertensive-like pattern described above (Cases 3, 8, 11, 13, and 14), (b) one showed a deep Q_3 and an inverted T_3 (Case 10), and (c) the other three showed electrocardiograms which were normal except for left axis deviation (Cases 7, 9, and 20). In four of the nine (Cases 3, 7, 8, and 10), tracings made before the attack are available for comparison. In every one of the four, the electrocardiogram after

healing resembles very closely the tracing taken before the attack except for a reduction of S_4 in Case 7.

Thus the evidences of acute infarction may disappear rapidly, leaving a partly healed lesion with no diagnostic electrocardiographic signs. Moreover, all evidences that an infarct ever occurred may disappear after healing; the tracing usually returns to its former contour; if it was normal originally, the final electrocardiogram may be normal.

This is not unexpected when one considers the electrocardiographic behavior of infarcts in general. When infarction heals: (a) The QRS complex changes which it produced tend to persist, but lateral infarction has none of these. (b) The T-wave in each lead tends to assume a direction opposite to that of the former RS-T interval deviation, but in acute lateral infarction the RS-T interval deviations are opposite in direction in each lead to normal T-waves. Consequently, they tend to give place to normal T-waves with the passage of time.

DISCUSSION

For a good many years lateral infarction was a confusing factor in the electrocardiographic study of coronary occlusion. Occasionally we saw patients with this type of tracing who gave a history of cardiac pain. However, we saw patients with similar electrocardiograms in whom auricular fibrillation was present, and to whom digitalis had been administered. The first definite clue came in December, 1934, when the patient described as Case 1 appeared and demonstrated that this electrocardiographic pattern could be caused by infarction of the lateral wall of the left ventricle, in the absence of auricular fibrillation or digitalis medication. The second clue was obtained when all cases in which cardiac pain was accompanied by this type of tracing were reviewed. Then the unexpected fact appeared that in this group of cases of coronary occlusion the incidence of auricular fibrillation was high. The third step was to review all cases with electrocardiograms of this sort in which the pattern of the tracing had been attributed to digitalis administration. Then it was discovered that all patients with electrocardiograms like that shown in Fig. 1*B* had clinical evidences suggestive of recent coronary occlusion.

The establishment of the fact that a lateral infarct may cause this type of electrocardiogram has removed an important source of diagnostic confusion. On the basis of electrocardiographic study during the acute stage, most large infarcts may now be classified as anterior, posterior, lateral, or combinations of these types. However, the establishment of the electrocardiographic pattern of lateral infarction has accomplished more than this. By making possible the study of a group of these cases, it has elucidated certain pitfalls in diagnosis, knowledge of which is essential if the costly mistake of overlooking a coronary thrombosis is to be avoided.

In three types of patients with lateral infarction there is very real danger of failing to recognize that coronary occlusion has occurred. (1) The case which is most confusing is that in which the lateral infarction is accompanied by auricular fibrillation, and digitalis is given before the electrocardiogram is made. The precordial discomfort is likely to be attributed to the arrhythmia, and the RS-T interval deviations to digitalis medication. (2) Another case which might give rise to dangerous misinterpretation is that of the individual with lateral infarction whose first electrocardiogram is not made until several days after the attack. If RS-T interval deviations have subsided and the tracing looks like that of a patient with hypertension, the original clinical impression of coronary thrombosis may be shelved while a dangerous search for a "better" diagnosis is conducted. (3) A third condition which might be misjudged is that of the patient who, three months after an attack of lateral infarction, is found to have an electrocardiogram which is normal except for left axis deviation. It would require a very typical clinical history to offset this negative finding in the minds of a good many physicians.

In the past six years we have come to lean quite heavily upon the electrocardiograph in the diagnosis of coronary disease. Because anterior and posterior infarctions often have characteristic signs during the acute, healing, and healed stages, we have been led to expect to find diagnostic, or at least suggestive, electrocardiographic findings after all major attacks of coronary thrombosis. This group of cases of lateral infarction shows that if the electrocardiographic method is leaned upon too heavily in diagnosis, it may prove a broken reed. The physician may obtain from it an unjustified, dangerous sense of security.

SUMMARY

Evidence is presented in this paper which suggests that acute infarction in the left lateral wall of the heart produces in the electrocardiogram a depression of the RS-T interval in Lead IV and usually a depression of this interval in Leads I and II. Lead III shows no characteristic abnormalities.

The RS-T interval deviation in Lead IV is often more marked when the precordial electrode is placed at or to the left of the apex than when it is put nearer the sternum.

The QRS complex is usually unaffected by lateral infarction. Consequently, the electrocardiographic pattern of this lesion can be reproduced by angina of effort.

Left circumflex artery thrombosis is usually responsible for infarction in the left lateral wall of the heart. However, when this vessel carries an unusually large part of the myocardial blood supply, its obstruction may give rise to more extensive infarction, with complex electrocardiographic patterns.

In some patients with lateral infarction there is very real danger of failing to recognize the fact that a coronary occlusion has occurred because (a) these patients frequently have auricular fibrillation, (b) digitalis action may produce a somewhat similar tracing, and (c) electrocardiographic signs of the lesion may disappear rapidly and completely.

The electrocardiographic method is a much less sensitive diagnostic procedure in lateral infarction than it is in anterior or in posterior infarction. Even when several precordial leads are used, a lesion in the left lateral wall of the heart, though incompletely healed, can escape detection.

On the basis of electrocardiographic study during the acute stage, it is now possible to classify most large infarcts as anterior, posterior, lateral, or combinations of these three types.

CASE REPORTS

CASE 1.—B. Z., a white man aged 54 years, was admitted to the Mount Sinai Hospital Dec. 22, 1934. He had suffered from effort angina for two years. A few days before admission, the attacks had increased in frequency and severity. At 3 A.M. on the day of admission a substernal and precordial pain began which radiated to both shoulders and both arms. It was worse than any he had ever had before. The pain was not relieved by the repeated administration of nitroglycerin, and only slightly ameliorated by two doses of pantopon.

On admission, at 12:45 P.M., the blood pressure was 88/66 (it had been 150 systolic prior to the present attack); the temperature was 97.8° F.; the pulse rate was 110 per minute; the respiratory rate was 32 per minute. The patient was dyspneic and cyanotic; the heart sounds were distant; coarse râles were heard in both lungs. The leucocyte count was 22,500 per cu. mm., and 88 per cent of the leucocytes were neutrophiles. The patient became steadily worse, developed pulmonary edema, and died at 11 P.M.

A necropsy was performed Dec. 23, 1934, by Dr. Meranze. The heart weighed 390 gm. It was normal in size and position. The left anterior descending coronary artery was atheromatous but had an "adequate lumen." The right coronary artery, though rigid, had a "good lumen." The left circumflex artery immediately after its origin showed marked reduction of caliber from former disease. At the point of narrowing, the remainder of the lumen was occluded by a red thrombus.

The heart muscle was flabby. There were fibrotic areas in the anterior surface of the left ventricle near the apex. A fresh infarct measuring 6 by 3 cm. was found in the "mid lateroposterior region of the left ventricle."

Two electrocardiograms are available (Fig. 1): *A*, a tracing taken June 14, 1933, eighteen months before death, which is essentially normal, and *B*, an electrocardiogram taken Dec. 22, 1934, shortly after admission, which shows marked R-ST interval deviations. The characteristics of this tracing differ from those seen in either anterior or posterior infarction. Lead IV-B shows a marked RS-T interval depression and a normal QRS complex. Leads I and II show a marked depression of the RS-T interval. Lead III shows a relatively normal ventricular complex without a significant Q-wave or a displacement of the RS-T segment. This patient received no digitalis.

CASE 2.—S. M., a white man 72 years old, with a history suggesting a coronary attack in 1936, came to the University of Pennsylvania Hospital Jan. 11, 1938, for lower abdominal symptoms. Dr. Ravdin operated to relieve a colonic obstruction

on Jan. 20, 1938. At 4 A.M. on Jan. 22, 1938, the patient had a severe attack of substernal pain. The heart became rapid (rate 180) and totally irregular. Morphine and 4 grains of digitalis were prescribed, and the patient was placed in an oxygen tent. The arrhythmia subsided in two hours. The pain gradually wore off, leaving a soreness. The patient felt "knocked out" afterwards, but the blood pressure did not fall. The significance of fever and leucocytosis was uncertain because the attack occurred during the postoperative reaction. There were several recurrences of pain on January 25 and 26, and the blood pressure fell from 200/100 to 90/55. Death, apparently cardiac, took place Jan. 27, 1938.

A necropsy was performed by Dr. Lippincott on the day of death. The left anterior descending coronary artery showed an organized obstruction, partly canalized, 6 cm. from its orifice. The right coronary artery was patulous but small and did not reach the posterior interventricular groove. The main channel of the left circumflex was patulous. One of its branches, low on the posterolateral surface of the left ventricle, was obstructed by a brown thrombus of recent origin.

The myocardium showed an area of healed infarction in the lower lateral surface of the left ventricle, with several small areas of fibrosis anterior to it. Since no definite recent infarction was visible grossly, a number of sections were cut from various portions of the left ventricular wall. On microscopic examination healed infarction was found in the areas where it had been visible to the naked eye. Recent degeneration of muscle fibers was found in all three sections taken from the lateral wall of the left ventricle. Some suggestion of recent degeneration was found in the anterior wall of the left ventricle, but not much. None was seen in the interventricular septum or in the posterior wall nearby.

No possible cause of death except the cardiac lesion was found.

Electrocardiograms were taken on January 22 (Fig. 2*A*), January 24 and 25, 1938. All were similar and resembled those in Case 1, except that left axis deviation was also present. The RS-T interval depression in chest leads CF_4 and CF_5 was not seen in lead CF_3.[1]

CASE 3.—J. S., a white man 53 years old, had attacks of severe substernal and upper abdominal pain lasting two hours each on Jan. 12 and 14, 1937. There were minor seizures in the interim. The blood pressure, known to have been 225/125 on Dec. 1, 1936, dropped to 140/70 after the attack. The blood sedimentation rate, which had been 10 mm. in one hour Dec. 2, 1936, became 24 mm. in one hour on Jan. 15, 1937. There was slight fever after the attack, but no leucocytosis. The clinical diagnosis was coronary thrombosis. The patient recovered, returned to work, and on Feb. 4, 1938, was reported to be alive and well.

Many electrocardiograms are available. One taken Dec. 2, 1936, while he was in the University of Pennsylvania Hospital on account of a small cerebral thrombosis, before he had had any cardiac pain, shows an inversion of T_1, a diphasic T_2, an upright T_3, an inverted T_4, left axis deviation, and no RS-T interval deviations. Electrocardiograms after the attack, shown in Fig. 2*D*, resemble those in Case 1. By Feb. 12, 1937, all RS-T interval deviations had disappeared, and the tracing had reverted to its former appearance. No digitalis was given to this patient.

CASE 4.—(This case was observed by Dr. E. Bruce Brooks, of Winston-Salem, N. C., and is reported here by reason of his courtesy.) Mrs. J. E. C., a woman 66 years of age, who had hypertension and angina of effort, suffered a severe attack of cardiac pain during the night of Dec. 19, 1936. Morphine was required. The blood pressure dropped from 200/120 to 90/70. Death occurred Dec. 24, 1936. Permission for necropsy was not obtained. Two electrocardiograms were taken, one on Dec. 20, 1936 (Fig. 3*A*), the other on Dec. 21, 1936. The patient did not receive digitalis.

CASE 5.—(This case was observed by Dr. Alexander Margolies, who has kindly permitted us to report it.) F. L., an ex-professional baseball player 57 years old, had had hypertension (160 to 210 systolic) for at least two years. On Nov. 11, 1935, while driving his car, he experienced pain in both arms and elbows. On the night of Nov. 24, 1935, a similar but much more severe attack occurred, accompanied by pain under the sternum and dyspnea. Morphine was administered. The next day the pain disappeared; the temperature was 99.6° F.; gallop rhythm was heard; an electrocardiogram (Fig. 3*C*) showed auricular fibrillation (which had not been present before the attack) and ventricular complexes like those in Case 1, with left axis deviation. The fever persisted for a few days. The blood pressure gradually fell to 150/100. The arrhythmia continued. The patient was digitalized after the electrocardiogram was taken. The clinical diagnosis was coronary thrombosis complicated by auricular fibrillation. On Dec. 19, 1935, the patient died suddenly. Permission for necropsy was not obtained.

CASE 6.—This case has been reported previously and the electrocardiogram has been published (Case 1, Fig. 24[12]). The patient was a woman 47 years of age who had hypertension and who developed auricular fibrillation in October, 1932. In January, 1933, she experienced several severe attacks of epigastric pain and an embolus lodged in her right ulnar artery. She died at home in February, 1933. The clinical picture was very suggestive of coronary occlusion, but on account of digitalis administration, and an "atypical" electrocardiogram, the diagnosis was uncertain. We now believe that she probably had a lateral infarction. Her digitalis dosage was relatively small. From Dec. 30, 1932, to Jan. 4, 1933, she received 1 cat unit t.i.d. From Jan. 4 to 18, 1933, she received 1 cat unit daily. All four electrocardiograms taken, Jan. 9, 12, 14, and 16, 1933, showed auricular fibrillation and ventricular complexes like those in Fig. 1*B*, with left axis deviation in addition.

CASE 7.—R. C., a white woman 48 years of age, came to the Hospital of the University of Pennsylvania May 13, 1932, on the service of Dr. George P. Muller. After careful study, including an electrocardiogram (Fig. 4*A*) and orthodiagram, we were uncertain whether she had gall bladder disease, coronary disease, or both. She gave a history of an attack suggesting a small coronary occlusion in 1930, after which she had substernal pain on effort. Cholecystectomy was done May 17, 1932. Gallstones were found. Convalescence was uneventful. On June 2, 1932, and again June 5, the patient experienced brief periods of syncope and precordial pain. Ten cubic centimeters of tincture of digitalis were administered between June 2 and 8, 1932, after which no more was given. On June 8, 1932, after lunch she had a major attack of pain over the heart which was referred to the left arm and was accompanied by vomiting, cyanosis, dizziness, and a cold sweat. After an hour, morphine was given and brought relief. The next day the leucocyte count was 11,200. Slight fever was noted occasionally from June 3 to 9. After the attack there was no definite change in blood pressure, pulse, or respiration. Gradual improvement took place, and the patient was discharged June 22, 1933. She has been followed in the Cardiac Clinic since that time. When last seen, Dec. 23, 1937, she had definite angina of effort and the blood pressure was 155/110, but there were no objective evidences of cardiac damage.

Many electrocardiograms were taken. The tracing before the attack (Fig. 4*A*) is normal except for left axis deviation. That on the day of the attack (Fig. 4*B*) resembles Fig. 1*B*. Within the first thirty-six hours the signs of acute infarction subsided, leaving T_1 and T_2 diphasic, T_3 flat, and T_4 inverted. Subsequent tracings (Fig. 4*C* and 4*D*) show a permanent reduction in the size of the S-wave in precordial leads. Otherwise the electrocardiogram looks just as it did before the attack. This reduction of the S-wave in Lead IV did not immediately accompany the acute attack. It occurred at some time between June 20, 1932, and March 30, 1933.

CASE 8.—G. S., a woman of 57 years, with a history of angina pectoris, came into the University of Pennsylvania Hospital Nov. 15, 1933, with hemoptysis and auricular fibrillation. There is no record of cardiac pain on this admission. She was digitalized. An electrocardiogram made Nov. 23, 1933, resembles that in Case 1, Fig. 1, except that left axis deviation was present. No precordial leads were taken. On Jan. 25, 1934, when she was readmitted because of glaucoma, she still had auricular fibrillation. From Jan. 27, 1934, to Feb. 4, 1934, 24 grains of powdered digitalis were administered. It was then stopped. On Feb. 5, 1934, the patient had a prolonged severe attack of precordial pain. The blood pressure dropped from 140/100 to 120/60. The leucocyte count rose from 7,600 on Jan. 26, 1934, to 15,000 on Feb. 7, 1934. The temperature was one degree above normal three times during the next few days. A consultant diagnosed coronary thrombosis.

The electrocardiogram made Feb. 6, 1934, resembles that in Fig. 1*B*, but because of digitalis medication it was not reported as showing evidence of coronary thrombosis. The patient improved and was discharged.

On May 1 and June 11, tracings were taken when digitalis effects were absent. T_1 was low, T_2 and T_3 were upright. Left axis deviation and auricular fibrillation were present. Chest leads were not taken.

The patient was last seen March 7, 1938. At that time an electrocardiogram showed auricular fibrillation, left axis deviation, more slurring of QRS, an inverted T_1 and normal T-waves in all other leads. Cardiac pain was not an outstanding symptom at this time because her activity was limited by her poor eyesight.

CASE 9.—J. B., a white male of 66 years, had experienced precordial pain for several months. On Dec. 9, 1933, he came to the University Hospital for a prostatectomy by Dr. Alexander Randall. Digitalis in doses of 1½ grains t.i.d. was started on the day of admission and was continued until December 27. On December 13 the patient had a severe precordial pain which lasted all night. The blood pressure dropped from 160/90 to 135/80, and later to 104/60. Cyanosis, fever, leucocytosis, and right basal râles appeared, and the patient looked "knocked out." He recovered, had his prostate removed Jan. 30, 1934, experienced an attack of auricular fibrillation from Feb. 2 to 4, 1934, and was discharged February 24. When last seen, Nov. 4, 1935, he had had cardiac pain after chopping wood, and showed a few extrasystoles.

Many electrocardiograms were taken. The first, Dec. 20, 1933, during the acute stage, looked like Fig. 1*B* with less RS-T interval deviation in Leads I and II and with left axis deviation. On Dec. 27, 1933, RS-T interval deviations were more pronounced. By Dec. 29, 1933, they had subsided markedly, and on Jan. 2, 1934 they had disappeared. The tracing was normal except for left axis deviation on Jan. 10, 1934, and Jan. 22, 1934. On Feb. 4, 1934, it showed auricular fibrillation with a small T_1 and T_2 and inverted T_4. On April 17, 1934, and Nov. 4, 1935, it was normal except for left axis deviation.

CASE 10.—W. C. was a white male who developed angina pectoris in 1918 at the age of 50 years; it continued until his death, June 30, 1934, at the age of 66 years. At necropsy, July 1, 1934, the left anterior descending coronary artery was small but patent. The lumen of the right coronary artery was obliterated at two different points by organized thrombi: the first was 2 cm. from its orifice, and the second was in the posterior descending artery. The left circumflex artery was large. Its lumen was occluded 2 cm. from its origin by an organized thrombus. No fresh thrombi were found in the coronary arteries. The left ventricular wall at the extreme apex was very thin and fibrous. The ventricular septum and the posterior wall of the left ventricle showed marked scarring, undoubtedly as the result of a former infarct. The whole heart was flabby. The posterior surface looked more reddish and felt softer than the rest. The heart weighed 540 gm.; its chambers were dilated; there were no valve lesions.

From the time when this patient first came under our care, Jan. 8, 1931, until his death, he kept in close contact with us, and many electrocardiograms were taken, probably about fifty in all. From the standpoint of the present paper, the following facts should be mentioned: (1) When he first appeared there was a deep Q_3 in his electrocardiogram. He probably had a healed posterior infarct at that time. (2) He experienced repeated paroxysms of auricular fibrillation. The first occurred in September, 1931, and brought on anginal pain. On Jan. 13, 1934, he had a paroxysm without cardiac pain. On May 10, 1934, another attack of auricular fibrillation occurred without anginal pain except during effort. The pain was relieved by nitroglycerin and rest, though the arrhythmia persisted. (3) He experienced three major attacks of cardiac pain which might have been due to cardiac infarction. The first occurred Nov. 24, 1932. It lasted eleven hours and was accompanied by auricular fibrillation. The patient was hospitalized until Jan. 16, 1933, and treated for coronary occlusion. Electrocardiograms showed a marked RS-T interval depression in chest leads and suggestions in the limb leads of fresh posterior infarction. The second is the one during which we believe the circumflex thrombosis may have occurred. On the morning of April 24, 1933, after having had many severe anginal attacks in the preceding twenty-four hours, he was seen in the cardiac clinic. The rhythm was normal. Nothing definitely new was found, and he was sent home to rest. At 1 P.M. very severe anginal pain began which was not relieved by three doses of nitroglycerin. He was brought to the Hospital of the University of Pennsylvania that afternoon, pale, cyanosed, and in a cold sweat. The blood pressure, formerly 155/90, was now 110/80. He had auricular fibrillation with a ventricular rate of 150, but his appearance was very different from that which he presented during former and subsequent paroxysms of the same arrhythmia. An electrocardiogram showed ventricular complexes like those in Fig. 1*B*, except that the Q_3 which had been present before was still there.* The next day the fibrillation stopped; the RS-T interval deviations diminished in size, but they did not disappear until April 25, 1933. For a month the contour of the electrocardiogram kept changing. No fever or leucocytosis occurred. The patient recovered and was discharged May 26, 1933. The third attack of cardiac pain was initiated by strenuous effort on June 26, 1934, and lasted until death on June 30, 1934. During this final episode, auricular fibrillation came and went. Marked RS-T interval deviations appeared in the electrocardiogram, and the blood pressure dropped to 80/60. This may have been an example of cardiac infarction without recent coronary occlusion.

Digitalis was never given to this patient except (a) from July 28 to Aug. 3, 1932, when he received 21 grains of powdered leaf, and (b) on June 30, 1934, when he received 24 c.c. of the tincture.

CASE 11.—F. K. was a mildly diabetic white man 58 years old. On Jan. 23, 1934, he had a severe substernal pain; then he developed cough, fever, leucocytosis, tachycardia, basal râles, and distant heart sounds. He was admitted to the Philadelphia General Hospital Jan 26, 1934, on the service of Dr. Dillon. At first there was some doubt whether the patient had coronary occlusion or a pulmonary infection. However, recurring severe attacks of substernal pain finally convinced the attending physician that the diagnosis of coronary occlusion was correct. Many electrocardiograms (22 in all) were taken. The one here reproduced (Fig. 3*B*) was obtained Feb. 3, 1934, two days after the most severe attack of all. Left axis deviation was present. The patient gradually improved. RS-T interval deviations had subsided markedly by Feb. 16, 1934. On Feb. 24, 1934, they had disappeared completely, leaving a tracing with T_1 and T_2 diphasic, T_3 and T_4 normal, and left axis

*The electrocardiograms in a similar case have been published.[4] The patient had a significant Q_3 before and after a possible lateral infarction.

deviation. The patient was discharged April 3, 1934. At present he has angina of effort. No digitalis was administered at any time.

CASE 12.—J. McH. was a white man 68 years old who developed severe substernal pain Sept. 21, 1931, which was accompanied and followed by all the clinical signs of coronary thrombosis. On Sept. 28, 1931, his physician, Dr. Henry Wise, asked us to take an electrocardiogram. The tracing has certain resemblances to that in Case 1, with, in addition, left axis deviation. The patient recovered and returned to work on a limited schedule on Oct. 3, 1932. On March 5, 1938, he was somewhat incapacitated as a result of two attacks of cerebral thrombosis in 1937. His heart has "given him no further trouble." No digitalis was given before the tracing was taken.

CASE 13.—M. C., a white man of 62, had an attack of coronary occlusion Nov. 1, 1932, and a recurrence of pain Dec. 5, 1932. Digitalis, in doses of 10 drops t.i.d., was begun after the second attack. An electrocardiogram which was taken Dec. 19, 1932, resembled Fig. 1*B*. Left axis deviation was also present. Digitalis was stopped; recovery took place, and Feb. 9, 1933, another tracing showed almost complete disappearance of RS-T interval deviations. He is reported to have died Dec. 10, 1934, as a result of his "heart lesion complicated by a kidney and bladder infection."

CASE 14.—T. C., a white man aged 50 years, had suffered with coronary symptoms for two years. In November, 1935, a marked exacerbation occurred. An electrocardiogram made Dec. 6, 1935, showed changes resembling those in Fig. 1*B*. On Dec. 9, 1935, he was referred to the Medical Ward of the Philadelphia General Hospital, on the service of Dr. Schnabel, with the diagnosis of "hypertension, angina, and possible coronary occlusion." There was a marked difference between the blood pressure in the two arms, but no signs of aortic aneurysm were elicited. By December 11 RS-T interval deviations had subsided considerably. In a tracing taken December 31, they were absent. T_1, T_2, and T_4 were inverted. Slight left axis deviation was present. He recovered and was discharged Jan. 4, 1936. No digitalis was administered.

CASE 15.—M. F. was a white man 74 years old who had a cystotomy for acute retention Sept. 4, 1935, in the Philadelphia General Hospital, on the service of Dr. Jump. After operation he complained of precordial pain, tachycardia developed, and the blood pressure changed from 130/80 to 100/80. He grew weaker and died Oct. 7, 1935. Digitalis was administered from Aug. 23, 1935, to Sept. 23, 1935; from August 23 to 29, the dose was 4 grains daily; from August 29 to September 4, 2 grains daily; and thereafter 3 grains daily. The only electrocardiogram was taken Sept. 19, 1935. It resembles Fig. 1*B* with left axis deviation in addition. The report of this tracing states that it was not possible to tell whether the RS-T interval deviations were due to coronary occlusion or to digitalis. The cause of this patient's death was apparently not clearly understood at the time. Review of the history and findings makes us feel that he probably had a lateral infarction shortly after operation.

CASE 16.—J. Y., a white man aged 59 years who was known to have hypertension, suffered an attack of pain in the chest and epigastrium, accompanied by dyspnea, on Jan. 9, 1936. He was admitted to the Philadelphia General Hospital on the service of Dr. Schnabel on Jan. 11, 1936, with tachycardia and slight fever. The blood pressure did not drop. An electrocardiogram which looks like Fig. 1*B* was taken January 13. Digitalis in doses of 2 c.c. daily was begun January 15. On January 17 the RS-T interval deviations had decreased in amplitude. Digitalis

was increased to 3 c.c. daily on March 3, 1936, and to 4 c.c. daily on March 12. On March 15 it was reduced to 3 c.c. daily and continued at this dose until discharge. The third tracing was taken March 16, 1936, when, on clinical grounds, the patient's lesion was thought to be quite well healed. In this electrocardiogram, however, the typical pattern of acute lateral infarction is seen, with RS-T interval deviations which are more marked than those on Jan. 17, 1936. The patient was discharged March 27, 1936, with a markedly reduced exercise tolerance. Later, he went into congestive failure and died Feb. 10, 1937.

CASE 17.—M. G., a white man 53 years old, had been rejected for insurance at the age of 41 because of a heart murmur, but except for a little dyspnea on effort he had been subjectively well until June 8, 1933. That afternoon, while at work, he had a severe attack of substernal pain, experienced rapid, irregular palpitation, became weak and short of breath, and thought he would die. He lay down for two hours. When he tried to get up, constriction over the heart and dyspnea occurred. Subsequently the systolic blood pressure fell 25 mm. and slight fever appeared. "Small doses" of digitalis were given for the next three days. An electrocardiogram (Fig. 7*A*), which was taken June 12, 1933, showed auricular fibrillation with ventricular complexes like those of Fig. 1*B*. He was admitted to the Philadelphia General Hospital June 12, 1933, on the service of Dr. Robertson. Between June 12 and 17 11 c.c. of tincture of digitalis were given. On the latter date the tracing (Fig. 7*B*) showed a slower ventricular rate and a disappearance of RS-T interval deviations. Digitalis was continued in doses of 4 c.c. of the tincture daily from June 18 to 24, and 3 cat units of powdered leaf daily from July 2 to August 14. The patient showed no toxic symptoms. He improved gradually and was discharged Aug. 14, 1933. On Aug. 10, 1933, clinical evidence suggested that the infarct had healed. Nevertheless, an electrocardiogram on that day (Fig. 7*C*) showed the most marked RS-T interval deviations of all. The typical pattern of acute lateral infarction was present. After discharge the patient led a restricted life with a markedly reduced exercise tolerance. Three years later he had another severe attack of cardiac pain and developed signs of congestive heart failure. Slow improvement took place for two weeks. Then, on Aug. 13, 1936, sudden death occurred with symptoms suggesting cerebral embolism. There was no necropsy.

There was a great deal of discussion as to whether the patient had an attack of coronary occlusion June 8, 1933, or merely a paroxysm of auricular fibrillation. The clinicians in charge were convinced that a coronary occlusion had occurred. The electrocardiographer was uncertain because the RS-T interval deviations "resembled digitalis effects" and because they were reproduced later by digitalis administration. Unless this patient actually had a coronary thrombosis June 8, 1933, it is difficult to explain the marked permanent reduction of exercise tolerance, the very slow recovery, or the reduction in size of the RS-T interval deviations between June 12 and 17, 1933, when the dose of digitalis was increased.

CASE 18.—I. L., an elderly white man, began to suffer recurring attacks of pain in the left chest about the middle of March, 1935. Some were referred to the right shoulder and arm, and lasted an hour. He was admitted to the Philadelphia General Hospital on the service of Dr. English, April 29, 1935, with epigastric pain, a rapid irregular pulse, slight fever, and a blood pressure of 150/70. The patient subsequently became psychotic. On May 14, 1935, he spent a violent night. The next day he was cyanosed and in shock with a blood pressure of 50 systolic and a heart rate of 30. On May 16, 1935, he died suddenly. There was no necropsy.

From April 29 to May 3, 1935, 4 c.c. of tincture of digitalis were given daily. On the latter date an electrocardiogram was taken which showed auricular fibrillation and ventricular complexes like those in Fig. 1*B*. On May 6 the interne made a

note that he had expected the electrocardiogram to show evidences of coronary occlusion, whereas the report showed only auricular fibrillation and digitalis effects. Tracings taken May 14 and 15, after his collapse, showed normal rhythm and signs suggesting infarction in the posterior surface of the left ventricle.

CASE 19.—G. E., an Armenian male of 54 years, had complained of increasing dyspnea and palpitation for the preceding year. On March 16, 1938, he was admitted to the University of Pennsylvania Hospital on account of lower abdominal pain. After considerable study, a tentative diagnosis of a small mesenteric thrombosis was made. At 10 A.M. on March 25, 1938, a severe epigastric and substernal pain began, and the blood pressure fell from 205/130 to 90/70. The pulse became weak and showed an extrasystolic arrhythmia. The patient became cold, weak, cyanotic, dyspneic, anxious, and sweaty. During the next few days there were slight fever and leucocytosis. The blood pressure slowly regained its former level over a period of three days. The acute episode subsided and the patient signed his release on March 31, 1938.

An electrocardiogram made March 25 (Fig. 2*B*), four hours after the onset of the attack, showed signs suggesting acute lateral infarction with left axis deviation. By the next day (Fig. 2*C*) the evidences of acute infarction had disappeared. No digitalis was administered to this patient.

The rapid disappearance of the evidences of acute myocardial ischemia in this case suggests that considerable constriction of collateral vessels may have accompanied the original coronary occlusion. There may have been a large area of temporary ischemia on March 25 and only a small area of permanent damage on March 26.

CASE 20.—B. C., a white man of 52 years, had an attack of severe substernal pain on March 6, 1938, which radiated to the neck. After he received ½ gr. of morphine, his heart "stopped beating for a minute," and the physician thought the patient was dead, but he recovered. On March 7 slight fever appeared. On March 9 another severe attack of pain occurred, and he was admitted to the Philadelphia General Hospital, on the service of Dr. Schaeffer, with tachycardia, a blood pressure of 100/80, cyanosis, basal râles, leucocytosis (12,000), and no fever. Another pain occurred March 16. Thereafter he improved slowly but steadily. He received no digitalis at any time. A number of electrocardiograms were taken. On admission the ventricular complexes resembled those in Fig. 1*B* except that left axis deviation was present, and the RS-T interval deviations in limb leads were less marked. By March 16 RS-T interval deviations had disappeared, T_1 and T_4 were inverted. On March 30 the electrocardiogram was entirely normal except for left axis deviation.

CASE 21.—M. N. was a white man of 33 who, in November, 1933, began to have attacks of burning pain in the epigastrium and substernal region, produced by effort and relieved by rest. These continued until his admission to the University of Pennsylvania Hospital May 15, 1934. On account of his youth, the diagnosis of angina was scarcely credited by the physicians in charge and the patient was sent to the electrocardiographic room May 19, 1934, with a request that tracings be taken before and after exercise. The control tracing taken at 4:05 P.M. (Fig. 5*A*) is normal. The patient then induced lower sternal burning discomfort of moderate degree by stepping up on a chair twenty-five times and then swinging the arms a few times. During this discomfort, at 4:15 P.M., the electrocardiogram shown in Fig. 5*B* was taken, and it shows the typical pattern of lateral infarction. By 4:29 P.M. the discomfort had subsided completely. At 4:35 P.M. the tracing had returned to normal (Fig. 5*C*). There never was any suggestion that this episode was anything but an attack of effort angina. Electrocardiograms taken subsequently, on May 23

and 31, 1934, and July 12, 1934, were all within normal limits. The patient is reported to have dropped dead in a bus in August, 1934. Similar electrocardiograms obtained during transient myocardial ischemia have been reported by Jervel[5a] and by Levy, Barach, and Bruenn.[5b]

CASE 22.—R. Z. was a woman of 42 years who had had diabetes eighteen years, since 1920. She began to suffer with intermittent claudication in 1930. In 1935 dyspnea and palpitation on effort appeared, and hypertension was discovered. In November, 1936, the patient had a few fainting spells. On March 1, 1938, mild precordial discomfort appeared on effort. On March 25 she was brought to the University of Pennsylvania Hospital in an acute attack of coronary occlusion, which probably began early that morning. She was cold and clammy. The blood pressure was 110/70. The pulse rate was 104 per minute. The next day she was a little better; the leucocyte count was 23,000, and there were râles in the lungs, especially on the left side. On March 27 she had a paroxysm of auricular fibrillation which lasted from 10 A.M. to noon, and the blood pressure dropped to 75/55. That night she had several attacks of severe dyspnea, and became stuporous. On the morning of March 28 she was again found to have auricular fibrillation. At 9:45 A.M. an attack of pulmonary edema brought about her death within fifteen minutes.

Necropsy was performed by Dr. Lippincott on March 28, 1938. The heart was of normal size. The right coronary artery was sclerosed but patent. The left anterior descending artery was occluded by organized calcified tissue. The circumflex artery was markedly narrowed 1 cm. from its origin by chronic atherosclerosis. At this point a recent red thrombus occluded the remainder of the lumen. An extensive area of infarction involved the upper half of the anterior surface of the left ventricle and the entire lateral wall, extending around well into the posterolateral region. It did not quite reach the interventricular septum posteriorly. The posterolateral portion of the infarction involved the inner half of the ventricular wall, leaving the epicardial surface relatively undamaged.

Electrocardiograms were taken March 25 and 26, 1938. On the first day (Fig. 6*A*) the limb leads showed a pattern suggesting acute anterior infarction. The precordial leads, however, were unusual: CF_3 showed an RS-T interval depression, suggesting posterior or lateral infarction; CF_4 showed a normal ventricular complex; CF_5 (in which the exploring electrode must have been considerably to the left of the apex, since the heart was not enlarged) showed a Q-wave and a marked RS-T interval elevation. On the following day (Fig. 6*B*) the pattern in the limb leads, though slightly different, was even more definitely that of anterior infarction. The precordial leads had changed markedly: CF_3 and CF_4 now showed a deep Q-wave and an elevated RS-T interval; CF_5 showed a much greater RS-T interval deviation than CF_3 or CF_4. Thus in neither of the tracings were the findings in precordial leads those of typical anterior infarction. On the first day the diagnosis of anterolateral infarction was made on the basis of the electrocardiogram. On March 26 the changes which had occurred since the day before suggested to us the possibility that the lesion had extended further forward into the anterior wall of the left ventricle; and that by dominating the RS-T interval deviation in CF_3 it had obscured the evidences of lateral infarction in this lead which had been seen on the previous day.

CASE 23.—J. S., a white man 59 years old, had hypertension and arteriosclerosis. On Jan. 10, 1938, he began to have epigastric pain, anorexia, cough, expectoration, dyspnea, orthopnea, and attacks of palpitation. He was admitted to the Philadelphia General Hospital on the service of Dr. Thomas Klein, on Jan. 18, 1938, looking very ill. The blood pressure had fallen from an earlier level of 200/100 to 105/75; the leucocyte count was 18,600; there were evidences of congestive heart failure. On Jan. 24, 1938, death occurred during a recurrence of cardiac pain.

A necropsy was performed that day by Dr. Ehrich. The heart was moderately enlarged. The left anterior descending artery was occluded 1 cm. from its origin by an old thrombus. The right coronary artery was very small. The left circumflex, a very large vessel, which continued on to form the posterior descending artery, was occluded 2 cm. from its origin by a recent thrombus. There was acute necrosis of the entire posterior and lateral wall of the left ventricle and the posterior third of the interventricular septum. The infarct extended from apex to base and from ventricular septum to the anterolateral portion of the ventricle—a very large lesion. In addition there was a large healed infarct in the anterior surface of the left ventricle, involving also the anterior part of the interventricular septum.

Electrocardiograms were taken Jan. 19, 20, and 21, 1938. The first shows a peculiar type of tachycardia, probably ventricular. The second (Fig. 6*D*) and third show a pattern much like that in Case 1, except that in Lead III there are a Q-wave, an elevated RS-T interval, and an inverted T-wave. The tracing shows a combination of the electrocardiographic signs of posterior and lateral infarction. The patient received 4 grains of powdered digitalis on Jan. 18, 1938.

CASE 24.—N. G. was a man of 69 years, a patient of Dr. P. Boland Hughes and Dr. Kendall A. Elsom. We are indebted to them for the privilege of reporting his findings.

On Dec. 17, 1937, the patient experienced a severe epigastric pain which radiated to the lower abdomen. It lasted from two to three hours, made him sweat, and caused him to feel distended. After the pain left, a soreness in the epigastrium persisted, and he felt short of breath, even when lying still. Examination showed slight cyanosis, a few basal râles, and a blood pressure of 120/80. On Dec. 23, 1937, there was a recurrence of epigastric pain and dyspnea. That day a transient but very definite pericardial friction rub was heard at the apex. On Dec. 26, 1937, urinary retention occurred. On Dec. 28, 1937, a left-sided pulmonary lesion was suspected. On Jan. 3, 1938, he seemed to be improving. That morning at eleven o'clock he had a sudden attack of dyspnea, cyanosis, and sweating. The pulse became imperceptible. At 4:30 P.M. a similar attack occurred which proved fatal.

A necropsy was performed by Dr. Lippincott on the day of death. The heart was not enlarged. The left anterior descending coronary artery was obstructed 3 cm. from its origin by calcified tissue. The right coronary artery was completely occluded 3 cm. from its origin by an old thrombus. The left circumflex artery was a very large vessel. In an upper branch an old calcified obstruction was found. The main vessel was blocked 2 cm. from its origin by a recent red thrombus. There was a large infarct involving the posterior and lateral surfaces of the left ventricle. The septum was scarred but had no fresh infarction. The anterior surface of the left ventricle showed a small scar but no recent muscle damage.

Electrocardiograms were taken four times. On Dec. 20, 1937, the tracing was normal. On Dec. 23, 1937, the RS-T interval was slightly elevated in Leads II and III and depressed in Lead IV. On December 24 these deviations were less marked. On Dec. 29, 1937, the last tracing was taken; it showed definite RS-T interval deviations in Leads II, III, and IV (Fig. 6*C*). No digitalis was administered at any time.

CASE 25.—C. D., a white man of 49 years, had been drinking heavily for two years and had developed psychotic tendencies. On Nov. 11, 1937, while walking on the street, he experienced a severe substernal pain which radiated to the left arm and epigastrium. Vomiting, dyspnea, and palpitation occurred. He was taken home and given morphine. Subsequently cough and hemoptysis developed. He was admitted to the Philadelphia General Hospital on the service of Dr. Burr Nov. 17, 1937, cyanosed, dyspneic, and psychotic. The blood pressure was 110/65. The heart was totally irregular. Several physicians who saw him agreed that the

arrhythmia was due to auricular fibrillation. A loud apical systolic murmur and a few basal râles were heard. The next day the rhythm of the heart became regular, and the patient's general condition improved somewhat. On Nov. 21, 1937, at 7:30 A.M., a severe attack of substernal pain occurred. The patient became dyspneic, the lungs congested, and the pulse weak and rapid; the blood pressure fell to 75/50. The patient rallied again. On Nov. 26, 1937, cardiac arrhythmia reappeared. On Nov. 30, 1937, the patient died, presumably from "rheumatic heart disease."

Necropsy was performed by Dr. McCutcheon on the day of death. A "buttonhole" mitral stenosis was found. The entire pericardium showed fresh pericarditis. The right coronary artery was small but patent. The left anterior descending artery was of normal size and patent. The left circumflex, a very large vessel which continued on to form the posterior descending artery, was occluded 1 cm. from its origin by a red thrombus. A large recent infarct involved the entire posterior surface of the left ventricle.

Electrocardiograms were taken Nov. 18 and 23, 1937. The limb leads showed right axis deviation, notched P-waves, and upright T-waves. The patient received 8 c.c. of digalen intramuscularly on Nov. 22, 1937, 2 c.c. on Nov. 23, 1937, and a daily dose of 1½ grains of powdered leaf thereafter. It is surprising that the only electrocardiographic evidence of this large infarct was the depression of the RS-T interval in Lead IV.

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THE HEART IN PNEUMOCONIOSIS*

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ALTHOUGH pneumoconiosis has received much attention in recent literature as the most important industrial disease of today,[1] relatively little has been said concerning the associated cardiac change, namely, cor pulmonale (pulmonary heart disease).

A brief review of the pathology of pneumoconiosis will explain why cor pulmonale occurs. The pneumoconioses (*pneumon*—lung; *konis*—dust) are caused by the inhalation of minute particles of organic or inorganic dust. In recent years it has become recognized that probably the only substance producing changes of clinical significance is free silica (SiO_2). Most of the silicates are harmless except asbestos (magnesium, calcium silicate), which produces asbestosis. Coal dust and metallic dust seem to be of importance only if combined with free silica.[2] The particles of silica are phagocytized and carried into the lymph channels, which become obstructed. Silica stimulates fibrosis. The fibrous tissue forms around the bronchi and small branches of the pulmonary arteries, and gradually replaces the lung tissue. Pneumoconiosis has been classified into three stages, according to the degree of fibrosis. Recently there is a tendency to substitute a more detailed pathologic roentgenologic classification.[3, 4]

Jaffe[2] stated: "The replacement of large parts of the lungs by a very poorly vascularized scar tissue and obliterating changes in the branches of the pulmonary artery interfere greatly with the pulmonary circulation. The increase in resistance to the blood flow causes hypertrophy of the right ventricle of the heart, the wall of which becomes thickened to from 6 to 10 mm. as compared with a normal thickness of from 3 to 4 mm. With the exhaustion of the reserve power the hypertrophic ventricle becomes decompensated and failure of the right heart is a common cause of death in advanced pulmonary silicosis."

With this in mind, we undertook to study the incidence of pulmonary heart disease in pneumoconiosis and its frequency as a cause of congestive failure. Second, we wished to ascertain whether the cardiac changes could be detected clinically and roentgenologically.

MATERIAL

Our material consisted of 205 cases of pneumoconiosis from the Los Angeles County Hospital. Of the 19,800 patients who came to necropsy

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in the last twenty years, 102 had pneumoconiosis. We included as pneumoconiosis cases of silicosis, anthracosis with moderate or marked fibrosis (anthracosilicosis), and pulmonary fibrosis in which the etiology was unknown provided the silica content of the wet lung tissue was more than 2.5 mg. per cent.[5]* There were also 103 other patients who had both an adequate history of exposure to silica and radiographs which showed the characteristic pulmonary changes of pneumoconiosis. In four of the patients who came to autopsy the clinical records were missing. We reviewed the roentgenograms in 105 cases in which they were still available.

ANALYSIS OF CLINICAL DATA

In the 201 cases in which histories were available, the disease was advanced; 55 were classified as moderately advanced (second stage), and 146 as far advanced (third stage). Most of the patients had been miners for a long period of years.

We found that pneumoconiosis is a disease of men past 40; in 31.5 per cent of the cases the patients were over 60 years of age, in 66 per cent over 50 years of age, and in only 8.4 per cent below 40 years of age. Cases of acute silicosis have been reported in young individuals after short periods of exposure.[6] One of our patients was less than 30 years of age, but he also had pulmonary tuberculosis.

Dyspnea was mentioned in 142 cases but could not be used as an index of cardiac involvement because it is also one of the cardinal symptoms of advanced pneumoconiosis. In 55.6 per cent of these cases dyspnea had been present for more than a year; in 27.5 per cent it had been noticed for over five years; and in one case had been present as long as thirty years. Cough was usually associated with the dyspnea and had had approximately the same duration.

On physical examination cardiac enlargement, as shown by palpation and percussion, was thought to be present in 23.8 per cent of the 201 cases. Auscultatory examination revealed that the heart sounds were distant in fifty-four instances (26.3 per cent). Cardiac murmurs occurred in twenty cases in which organic heart disease, other than cor pulmonale, was excluded.

Cor pulmonale is one of the types of heart disease in which the cardiac rhythm tends to remain normal throughout.[7] In this series auricular fibrillation occurred in six cases of pneumoconiosis in which cor pulmonale was apparently the only heart disease present. In two of these cases this was confirmed by electrocardiographic and autopsy evidence, respectively.

We believe that accentuation of the pulmonic second sound and the presence of marked cyanosis are suggestive of cardiac involvement in

*The microdeterminations were kindly done by Albert L. Chaney, Ph.D., chemist at the Los Angeles County Hospital.

pneumoconiosis. There was other evidence of cardiac failure in 63 per cent of the twenty-two cases in which the pulmonic second sound was accentuated. In 88 per cent of the twenty-seven cases in which there was marked cyanosis, other signs of cardiac failure were also present.

Serologic tests for syphilis were recorded in 166 cases, in 19.8 per cent of which the reaction was positive. This is approximately three times the general incidence of syphilis in the hospital population.

Diseases interfering with the pulmonary circulation are frequently thought to cause compensatory polycythemia. This was not substantiated by the findings in our series. The hemoglobin content and the erythrocytes were rarely increased, and not infrequently anemia was present. The hemoglobin content had been measured in seventy-two cases, and in only two (2.7 per cent) was it above 100 per cent. Some degree of anemia (hemoglobin below 80 per cent) was present in 45.8 per cent. The erythrocytes had been counted in seventy cases and were found to number more than 5,500,000 per cubic millimeter in only three instances (4.3 per cent), whereas in 18.5 per cent of the cases the count was below 4,000,000.

Electrocardiograms were available in 43 cases, in 20 of which an autopsy had been performed. Of these 43 cases, the axis deviation was right in 16 (37.2 per cent), normal in 19, and left in 8.

Right axis deviation closely paralleled the autopsy evidence of right ventricular hypertrophy. There were 10 autopsy cases in which right axis deviation had been present. Of these, pure right ventricular hypertrophy was found in 8, marked dilatation of the right heart without hypertrophy in one, and hypertrophy of both ventricles in one. In only one case in which there had been no abnormal deviation of the electrical axis was right ventricular hypertrophy found at autopsy, and in this instance pericarditis was also present.

The electrocardiograms in 24 cases of pneumoconiosis in which there was no known organic heart disease other than cor pulmonale showed evidence of myocardial damage in 9 (low voltage in 5 cases and inversion of T_2 and T_3 in 4 cases). Two other tracings showed auricular fibrillation.

CONGESTIVE FAILURE

The term "definite congestive failure" was reserved for patients who came to necropsy with marked chronic passive congestion of the liver and either ascites or edema, for cases in which the pathologist made a diagnosis of "congestive failure," and for living patients whose ascites or edema led to the clinical impression of "congestive failure." All patients in whom the evidence of congestive failure was less convincing, but suggestive, were classified as instances of "questionable failure."

We found that congestive failure occurs especially in the third stage of pneumoconiosis and is a rather common cause of death. To

determine the incidence of failure we divided the patients into two groups: (1) those living, according to last available records, and (2) those whose records showed that they died. There were eighty-four living patients in the total group, 10.7 per cent of whom had definite congestive failure. There were 121 patients who died, 48.8 per cent of whom had had definite congestive failure (Table I A). We also divided patients who had no evidence of cardiac involvement except cor pulmonale from those who had hypertension (blood pressure 150/100 or more) or organic heart disease other than pulmonary heart disease. Nine per cent of the sixty-seven living patients without heart disease other than cor pulmonale had definite congestive failure. Most of these were in the third stage of pneumoconiosis. Forty-seven and two-tenths per cent of the eighty-nine patients who died had had definite congestive failure. Nearly 80 per cent of these were cases of third stage pneumoconiosis (Table I B).

TABLE I

A. INCIDENCE OF CONGESTIVE FAILURE IN 205 CASES OF PNEUMOCONIOSIS

LIVING PATIENTS (TOTAL, 84)		DECEASED PATIENTS (TOTAL, 121)	
QUESTIONABLE FAILURE	DEFINITE FAILURE	QUESTIONABLE FAILURE	DEFINITE FAILURE
10.7%	10.7%	14.0%	48.8%

B. INCIDENCE OF CONGESTIVE FAILURE IN 156 CASES OF PNEUMOCONIOSIS WITHOUT HEART DISEASE EXCEPT COR PULMONALE

	LIVING PATIENTS (TOTAL, 67)		DECEASED PATIENTS (TOTAL, 89)	
	QUESTIONABLE	DEFINITE	QUESTIONABLE	DEFINITE
Stage II	4.5%	1.5%	2.3%	10.1%
Stage III	4.5%	7.5%	10.1%	37.1%
Total	9.0%	9.0%	12.4%	47.2%

The late occurrence of congestive failure in pneumoconiosis was further indicated by a study of the duration of the signs of congestive failure. In the group of fifty-three patients without heart disease other than cor pulmonale who died with congestive failure, its duration had been over two months in only two, three months in one, and seven months in the other. This evidence seems quite conclusive that cardiac failure is a terminal event and that when it occurs the prognosis is grave.

Our findings are not in agreement with the popular concept that 75 per cent or more of silicosis patients die of pulmonary tuberculosis.[8, 12] Definite congestive heart failure occurred more frequently in our patients than did tuberculosis. The sputum was examined in 103 cases and tubercle bacilli were found in forty-two (40.8 per cent).

In the autopsy material 41 of the 102 patients (40.2 per cent) had had tuberculosis, while 52 (51.0 per cent) had had definite congestive failure.

It has been thought that patients with anthracosilicosis are less susceptible to tuberculosis than patients with pure silicosis.[9] The comparatively lower incidence of tuberculosis in our series may be partially explained by the fact that some cases of anthracosilicosis were included.

RADIOGRAPHIC FINDINGS

We reviewed the radiographs which were available in 105 of our cases. In twenty-seven of these cases the lesion was verified at autopsy. An effort was made to determine the number in which cardiac enlargement was present and to learn whether or not we could confirm reports of constant changes in the posteroanterior (sagittal) cardiac shadow associated with right ventricular enlargement.

The right ventricle lies almost entirely on the anterior and diaphragmatic surfaces of the heart and does not of itself form any material part of the cardiac silhouette in the posteroanterior view. We recognize the value of lateral and oblique views in detecting right ventricular enlargement, as demonstrated by Fray,[10] Pancoast and Pendergrass,[3] Parkinson and Hoyle,[11] and others. Our material consists entirely of routine sagittal films, and therefore we are limiting our discussion to the findings in these.

The films were first reviewed independently. The findings were then compared with the clinical and pathologic data. The points covered were: (1) cardiac enlargement by inspection; (2) prominence of the pulmonary conus; (3) elevation of the apex; (4) prominence of pulmonary vascular shadows; (5) enlargement of the right auricle; and (6) cardiac measurements in longitudinal, basal, and transverse diameters, and the cardiothoracic ratio.

Enlargement by Inspection.—In each case the heart was classified as to its size and its type of enlargement according to the general impression gained from inspection of the films only. The pulmonary changes so obscured the heart shadow that in many cases the impression of cardiac size was unreliable, and in 4.7 per cent of the entire group absolutely no impression of cardiac size could be obtained.

Pancoast and Pendergrass[3] state: "It is a striking feature that advanced silicotics who have developed mild myocardial degeneration do not, as a rule, present the roentgenologic evidences of a large cardiac shadow in the sagittal view, but it may be demonstrated in the lateral direction." The overexpansion of the lung in silicosis makes the sagittal cardiac silhouette less reliable as a measure of cardiac size because of the increase in posteroanterior chest diameter and low position of the diaphragm. Lanza,[12] while admitting the theoretical basis for right heart hypertrophy, states that in pneumo-

coniosis large heart shadows are not seen in the films and that the heart often appears small and "hanging."

In 78 of the 105 cases in which radiographs were available the patients had no heart disease other than cor pulmonale. The findings in this group support the above statements. Right ventricular hypertrophy did not usually cause characteristic enlargement of the posteroanterior cardiac silhouette. The heart appeared definitely enlarged in 24.3 per cent of these 78 cases, but in only 5.1 per cent was the enlargement thought to be right ventricular.

From a study of the films in 27 autopsy cases, we found that all but one of 11 hearts weighing over 400 gm. were represented by recognizably enlarged silhouettes. Right ventricular hypertrophy was rarely determined by inspection of the routine posteroanterior films. Only 2 of 10 autopsy cases with right ventricular hypertrophy were identified as such by inspection of the sagittal films alone. The hearts in 5 of the 10 cases were considered radiographically normal; 4 of these hearts weighed 380 gm. or less.

These facts support our conclusions and the statements of others that right ventricular hypertrophy may be present without enlargement of the posteroanterior cardiac silhouette.

Prominence of Pulmonary Conus.—Enlargement of the pulmonary conus, the outflow channel of the right ventricle, has been mentioned as radiographic evidence of right ventricular enlargement. In a series of 127 cases of third-stage or advanced second-stage anthracosilicosis, Dyson[13] found enlargement of the pulmonary conus in 14 per cent and attributed it to right ventricular enlargement. In his single autopsy case this idea was confirmed. Numerous authors have pointed out the association of enlargement of the pulmonary conus with right ventricular hypertrophy in congenital and in mitral heart disease.

Our findings indicate that enlargement of the pulmonary conus, when present in pneumoconiosis, usually accompanies definite right ventricular hypertrophy. The pulmonary conus was seen to be definitely enlarged in approximately 22 per cent of the entire group of 105 cases. In 28.5 per cent this area was obscured by overlying pulmonary markings. In eleven cases with autopsy proof of right ventricular enlargement (in which films were available), the pulmonary conus was obscured in two. In five of the remaining nine cases the conus was definitely dilated. In one patient who came to autopsy the film showed dilatation of the conus and general enlargement of the heart, but the autopsy record failed to mention any abnormality in the heart.

Elevation of Apex.—Elevation of the cardiac apex should occur when the right ventricle, which constitutes the anterior and lower part of the heart, hypertrophies. In extreme cases this may lead to a typical *cor en sabot* such as is associated with certain congenital heart lesions.

However, Parkinson and Hoyle[11] failed to find this criterion of right ventricular hypertrophy in any of their cases of emphysema, and Dyson,[14] in his discussion of the roentgenologic appearance of the heart in anthracosilicosis, does not mention it. Our findings in this regard indicate that, although elevation of the apex is uncommonly seen in pneumoconiosis, when present it suggests right ventricular hypertrophy. In some cases it is difficult to determine the exact position of the apex without fluoroscopy.

Among the 27 cases of pneumoconiosis with autopsy records in which films were available, there were 10 with right ventricular hypertrophy. The apex was definitely elevated in 2, and slightly or questionably elevated in 3. It was also apparently elevated in one case with hypertrophy of both ventricles. In all autopsy cases in which the radiographs showed an elevation of the apex, the heart weighed at least 420 gm. and there was hypertrophy of the right or both ventricles.

Pulmonary Vascular Prominence.—Although Parkinson and Hoyle[11] found that prominence and tortuosity of the large branches of the pulmonary artery are the most frequent evidences of cardiac involvement in emphysema, we were unable to make use of this criterion in the radiographic study of pneumoconiosis because the pulmonary lesion blots out the vascular detail in most cases.

Enlargement of Right Auricle.—Our findings agree with those of Parkinson and Hoyle,[11] who logically regard enlargement of the right auricle as a late and rather unusual finding in cor pulmonale. This change, which alters the right cardiac border, appears therefore to be of little practical value.

*Measurements.**—The transverse diameter is one commonly used as a measure of cardiac size, but our findings, like those of Newcomer and Newcomer,[16] throw doubt on its value. Its value in pneumoconiosis is also questioned by Dyson,[14] who states that although practitioners in anthracite coal regions recognize cardiac failure as a frequent cause of death in pneumoconiosis, a definite lesion is not diagnosed clinically since there is no increase in the transverse cardiac diameter. Since the cardiothoracic ratio depends on the transverse diameter of the heart, it likewise is a poor criterion of cardiac enlargement. It was impossible to determine the various diameters in 12 to 18 per cent of the 105 cases (Table II).

Our findings lead us to believe that, of the diameters measured, the basal or broad diameter is the most sensitive index of right ventricular enlargement. This diameter was greater than the maximum normal in 47.5 per cent of the seventy-eight cases in which there was no cardiac disease other than cor pulmonale. This measurement was increased more often than any other, and the frequency of its increase

*Maximum and minimum normal figures for the various diameters were obtained from Levene and Reid.[15]

closely parallels the percentage of hearts with right ventricular enlargement found in the autopsy series of 102 cases. The cardiothoracic ratio, on the other hand, was above maximum normal in only 7.7 per cent of these seventy-eight cases (Table II).

The radiographic measurements in the group with heart disease other than cor pulmonale testified, as would be expected, to the presence of more advanced degrees of hypertrophy. Increased diameters, with the exception of the basal diameter, occurred more than twice as frequently in this group as in the group in which only cor pulmonale was present. The basal diameter was enlarged in only a slightly higher percentage in the former group of cases (59.2 per cent as compared to 47.5 per cent).

In the twenty-seven cases with both radiographic and autopsy records, the findings confirm the above observations. Although all cardiac diameters were above maximum normal in the large hearts (400 gm. or above), the cardiothoracic ratio was above maximum normal in only four of seven hearts which weighed over 500 gm. It therefore seems very unreliable as a criterion of cardiac enlargement. In the hearts weighing less than 400 gm. in which radiographic measurements were possible, all except the basal diameter were within normal limits. The basal diameter was increased in three of four cases of right ventricular hypertrophy in this group, and in only one case without right ventricular hypertrophy. The basal diameter, therefore, as previously stated, appeared to be the most sensitive index of right ventricular enlargement.

TABLE II

MEASUREMENTS OF THE HEART IN POSTEROANTERIOR ROENTGENOGRAMS OF 105 CASES OF PNEUMOCONIOSIS

	WITHOUT HEART DISEASE EXCEPT COR PULMONALE (%)	WITH OTHER CARDIAC DISEASE (%)
	(78 cases)	(27 cases)
Longitudinal		
Obscured	16.7	3.7
Above maximum normal (15.0 cm.)	25.6	59.3
Broad or basal		
Obscured	20.5	7.4
Above maximum normal (10.5 cm.)	47.5	59.3
Transverse		
Obscured	14.1	3.7
Above maximum normal (14.5 cm.)	11.5	51.8
Cardiothoracic ratio		
Obscured	14.1	3.7
Below minimum normal (1.92)	7.7	33.3

AUTOPSY FINDINGS

Among the 102 autopsy cases of pneumoconiosis, we found 29 with hypertension or organic heart disease other than cor pulmonale. They included 18 cases of hypertension, 5 of pericarditis, 3 of coronary

heart disease, 2 of rheumatic heart disease, and one case of thyrotoxicosis. This leaves 73 cases of pneumoconiosis without cardiac disease other than cor pulmonale.

Criteria of Hypertrophy.—Estimation of right or left ventricular hypertrophy is most accurately accomplished by weighing each ventricle separately.[17] Since only the cardiac weights and the mural thicknesses had been recorded by the autopsy surgeon, we were obliged to use the average thickness of the ventricular wall as a criterion of hypertrophy.

Hearts in which the right and left ventricular walls measured less than 4 mm. and not more than 12 mm. in average thickness, respectively, were considered normal. A right ventricular wall which averaged 5 mm., or a left ventricular wall which averaged over 15 mm. in thickness, was considered definitely hypertrophied. The term "hypertrophy of both ventricles" was used to designate hearts in which both right and left ventricles were definitely hypertrophied, and also hearts in which the wall of the right ventricle was 5-6 mm. and that of the left more than 12 mm. in thickness, or the wall of the right ventricle 6-7 mm. and that of the left more than 14 mm. Our criteria, therefore, restrict the term "right ventricular hypertrophy" to those hearts which have a *predominant* right ventricular hypertrophy. Although Thompson and White[18] found left ventricular strain to be the greatest cause of right ventricular hypertrophy, the great majority of their examples of right ventricular hypertrophy would have been listed, by our criteria, under "hypertrophy of both ventricles." We feel that in the group of cases without cardiac disease other than cor pulmonale the percentage of cases listed as "right ventricular hypertrophy" represents quite conservatively the percentage of cases of cor pulmonale caused by the pneumoconiosis. Our classification still leaves a small group of hearts with questionable hypertrophy of the right or the left ventricle which we classed as "questionably normal."

In some autopsy records, the thickness of the right ventricle or, rarely, of the left ventricle, was not stated. If not mentioned, we have considered the ventricle as normal. This added an unavoidable error, but one which would minimize and not overemphasize the effect of pneumoconiosis as a cause of right ventricular hypertrophy.

Ventricular Hypertrophy.—Exclusive right ventricular hypertrophy occurred in 44.1 per cent of the total of 102 autopsy cases of pneumoconiosis. Including those cases in which both ventricles were hypertrophied, the incidence of right ventricular hypertrophy was 58.8 per cent.

Among the seventy-three autopsy cases in which there was no heart disease other than cor pulmonale the incidence of exclusive hypertrophy of the right ventricle was 52.0 per cent; including those cases

in which both ventricles were hypertrophied, the incidence was 61.6 per cent (Table III). From these findings we feel justified in concluding that the right ventricle is hypertrophied either exclusively or together with the left ventricle in the majority of fatal cases of pneumoconiosis.

TABLE III

INCIDENCE OF VENTRICULAR HYPERTROPHY IN 102 AUTOPSY CASES OF PNEUMOCONIOSIS

	WITHOUT HEART DISEASE EXCEPT COR PULMONALE (%)	WITH OTHER CARDIAC DISEASE (%)	TOTAL (%)
	(73 cases)	(29 cases)	(102 cases)
Left	0.0	10.3	2.9
Normal	30.1	20.7	27.5
Normal (?)	8.2	17.2	10.8
Both	9.6	27.7	14.7
Right	52.1	24.1	44.1

Weight of Hearts.—The heart weight was increased in the majority of the cases of pneumoconiosis. The hearts in approximately two-thirds of the 102 cases weighed more than 350 gm. This is in accord with the findings of Sweany, Porsche and Douglass,[9] who found that in nearly all of their cases the heart weighed from 350 to 500 gm. and had a thick right ventricular wall. The very heavy hearts, those weighing above 500 gm., occurred more frequently in the patients with other associated cardiac disease than in those in which only cor pulmonale was present (Table IV).

TABLE IV

PERCENTAGE OF HEARTS IN VARIOUS WEIGHT GROUPS IN 102 AUTOPSY CASES OF PNEUMOCONIOSIS

HEART WEIGHT IN GRAMS	WITHOUT HEART DISEASE EXCEPT COR PULMONALE (%)	WITH OTHER CARDIAC DISEASE (%)	TOTAL (%)
	(73 cases)	(29 cases)	(102 cases)
300 or below	28.8	13.7	24.5
301-350	13.7	0.0	9.8
351-400	17.8	20.7	18.7
401-450	20.6	10.4	17.6
451-500	6.8	24.1	11.8
Above 500	12.3	31.1	17.6

SUMMARY AND CONCLUSIONS

1. Autopsy protocols of 102 cases of pneumoconiosis (occurring in nearly 20,000 autopsies), together with the clinical records of 103 additional cases in which there were adequate histories of exposure to silica and characteristic roentgenographic changes, were reviewed. This was done to determine the incidence of cor pulmonale (pulmonary heart disease) and congestive heart failure, and whether or not the cardiac changes could be detected clinically and roentgenologically.

2. At autopsy, right ventricular hypertrophy was found to occur in approximately one-half of the cases of pneumoconiosis. Exclusive right ventricular hypertrophy was present in 44.1 per cent of the total of 102 autopsy cases. Including hypertrophy of both ventricles, right ventricular hypertrophy occurred in 58.8 per cent of the cases.

3. Definite congestive heart failure was found more frequently in these cases (51 per cent) than was tuberculosis (40.2 per cent). It was usually a terminal event. Therefore, when it occurs clinically, the prognosis is grave. It may be concluded, furthermore, that if pneumoconiosis is uncomplicated by tuberculosis or other pulmonary infection death from cardiac failure is to be expected.

4. Our findings lead us to believe that the clinical diagnosis of cor pulmonale in pneumoconiosis is suggested by accentuation of the pulmonic second sound, marked cyanosis, right axis deviation in the electrocardiogram, and characteristic changes in the posteroanterior radiograph, namely, prominence of the pulmonary conus, elevation of the cardiac apex, and an increase of the broad or basal diameter, in the absence of enlargement of other diameters.

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THE SOCIAL COMPONENT IN HEART DISEASE*

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THE function of the heart as the core of the individual's life and strength has paramount significance for each human being. Damage to this essential life-maintaining organ constitutes a threat which varies in its menacing quality not only with the degree of severity of the disease, but with the individual emotional make-up. Potential sources of social difficulties exist in the very nature of heart disease itself: in the sudden danger of its acute phases, in the possibility of recurrence and progression, and in its chronicity. The incidence of heart disease in all age groups—in children, young adults, middle-aged and elderly persons—implies unfavorable influences in varying degrees upon all the activities of life.

In every cardiac service certain problems recur again and again; for example, there is the ambitious, capable adolescent removed from school and sport; the young adult wage earner in need of vocational rehabilitation and financial aid for dependents; the young widow with small children on marginal income; the individual permanently incapacitated for continued pursuit of a successful professional or industrial career. Many variations exist in these problems, even in cases in which the degree of heart damage and economic conditions are approximately the same. The points of difference among these patients lie frequently in the personal sphere, in the reaction of the patient to illness in general, to cardiac illness in particular, and in the neurotic gain the patient derives from the illness in relation to the various members of his family, his immediate associates, his work, and all of his other contacts. Equally significant factors in these problems often arise from the reaction of the various members of his family to the patient and his illness. Viewed from these angles, the treatment of heart disorders carries with it implications greater than mere medical therapy. Individualized evaluation of the patient in all of his significant relationships should be the focus of any effective plan of care.

The objectives for care of these patients will vary according to the stage of the illness at which recommendations for care are being made. Obviously, the primary aim for any particular patient will be restoration to a state of maximum well-being. Continuous thought will be given to prevention of recurrence, and retardation of progress, of the

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illness. When these can no longer be accomplished, efforts will be directed toward reduction of the individual's disabilities and palliation of the distress which results from chronic progressive disease. These objectives have their best chance of realization in clinics and hospitals where physicians and social workers function together with mutual understanding of immediate and ultimate aims and of their respective roles in assisting the patient to meet his problem.

This paper will approach the subject of the social component in heart disorders as they affect children, adolescents, and adults. The major emphasis in the consideration of the problems of children and adolescents will be on prevention. As to the problems of adults in whom the disease has already become established, attention will be focused principally on adjustments of the patient's life activities.

PROBLEMS OF CHILDREN AND ADOLESCENTS

Rheumatic heart disease is the most prevalent type of heart disease in children; it has been estimated that in this country about 80 per cent of all organic heart disease in children of school age is rheumatic.[1] Although the etiology of rheumatic fever is not yet known, environmental conditions of dampness, lack of sunlight, overcrowding, general poor physical hygiene, and inadequate nutrition seem to be contributory to its development. Of equal importance with the child's physical surroundings are the persons in immediate contact with him. During his early formative years the child is particularly susceptible to the emotional influences of his environment. Overanxiety of parents and relatives, deficiency in normal affectionate concern for the child, mismanagement in child training, family friction, or other tensions in the home may have an adverse psychologic effect of far-reaching consequence on the child's entire later life. The possibility or the advisability of care in the home during both the acute and chronic phases of his illness will be largely determined by all of these factors, so that they require thoughtful consideration on the part of physicians, nurses, and social workers responsible for the care of the patient.

A boy aged 14 years, convalescing from rheumatic fever, was discharged from a hospital to his home by a house officer on assurance by an apparently intelligent mother that she was able to carry out his recommendations for many months of complete bed rest.

The following week a social worker called to ascertain how the patient was adjusting himself. As she approached the suburban cottage, she heard gales of laughter and shouting. Passing by a low street-floor window, she saw the patient jumping about on his couch, surrounded by six or eight boys and an immense dog. The radio was on full blast. Just as she entered the house, the patient dashed out of bed to change the radio program and embrace the romping dog. No one else was at home.

The mother had been called to a hospital by the serious illness of her divorced husband, who was still dependent on her emotionally and financially.

While awaiting the mother's return, the worker observed great strips of wall paper separated from the wall because of dampness. The temperature of the house was so low as to chill the worker even in her heavy winter coat. Later it was explained that the melting snow had leaked into the cellar and had extinguished the furnace fire!

As the social worker studied the situation, she found a mother distraught by her former husband's illness, their continuing personal maladjustments despite divorce, the critical illness of a daughter in another hospital, the impending loss of their home, a long history of family friction, and the ever-present behavior problem of the patient, who had been for years impervious to any family effort at guidance.

Improvement under such conditions was unlikely following even the most ideal hospital care for rheumatic fever. This mother, though apparently intelligent and actually well intentioned, was neither emotionally, economically, nor physically equipped to meet this patient's needs. Considerable social case work, based on understanding of the emotional reactions of the members of this family and a knowledge of resources of the family and community, was required before this patient received adequate care away from home, with resulting arrest of his rheumatic disease and treatment of his personality difficulties. Complete bed rest with correct nutrition for a period of many months' duration in a peaceful, warm, dry, sunlit environment, with adequately supervised educational and recreational opportunities, was required for this patient. This is the optimum program for all patients. When it cannot be obtained or approximated in the home, a substitute home is recommended, either in an institution or adequate foster home, under expert medical, nursing and social direction.

Inactivity and separation from the daily school and play interests with friends lead inevitably to boredom and restlessness. Unhappy thrashing about in bed is not synonymous with complete rest.

The serious effects of loss of school work and lack of opportunities for development were exemplified in the case of a 22-year-old man admitted to a hospital for total thyroidectomy.[2] From the age of 8 years, rheumatic heart disease had deprived him of education, play, normal companionship, and regular occupation. Repeated exacerbations and a progressively increasing degree of cardiac involvement had finally brought him to a public infirmary with an extremely poor prognosis for life. His illness had gradually produced a taciturn, morose, ill-tempered youth with asocial tendencies. For a considerable time following his admission to the hospital for surgical treatment, all who were engaged in his care believed that they were dealing with a person of subnormal mentality. However, after total thyroidectomy, followed by clinical improvement, the conclusion was reached that his behavior and poor intellectual grasp were, in reality, the result of interrupted schooling and normal human relationships, general deprivation and lack of opportunity. An agreeable home, clothing, financial support, regular medical attention, re-education to life in a normal community away from hospitals and infirmaries, recreation, vocational guidance and placement, reassurance, and encouragement were all part of a social plan of treatment. As this treatment progressed, it yielded increasing evidence that the patient was an alert, intelligent, ambitious person, and, in the course of time, he made extraordinary progress in attaining an independent, contented, and self-maintaining existence.

The importance of a supervised plan of school studies, occupational therapy and recreation, gradually adjusted to the increasing capacity of the child, cannot be overemphasized. Some district nursing associations and women's organizations have furnished resources for occupational therapy and recreational facilities in the homes of children ill with heart disease. In Massachusetts the law[3] provides that the school committee of every town shall ascertain the number of physically handicapped children of school age unable to attend public school. The presence of five or more such children in any given town makes it obligatory for the committee to employ teachers for instruction in the individual homes or in institutions. If there are less than five children, the law is permissive. In certain instances in which children have had several years of institutional care for heart disease their continued school instruction has enabled them to meet the public school requirements for graduation. The admirable work for children with heart disease which has been undertaken in some states by the federal social security program could be extended with profit to other parts of the country.

Aftercare for children and adolescents with rheumatic heart disease is always a composite of adequate treatment and prevention. Proper attention to the first of these goals should result in the achievement of the other. Certain of the conclusions reached in a recent intensive study* of 1,000 children with rheumatic heart disease over a ten-year period are pertinent. From the point of view of prognosis, it is believed that the five or six years following the initial rheumatic infection are the most dangerous and difficult period. If patients pass through these years safely and do not develop moderate to severe rheumatic heart disease with cardiac enlargement, they will probably do well.† It is during this period that special emphasis must be put on medical supervision at regular intervals in order to detect the presence of rheumatic infection or the development of valvular damage. The most important single factor in aftercare is avoidance of infection, which needs repeated interpretation both to the patients and their families; patients are urged to isolate themselves from those who have colds, either at home or in the school. The importance of avoiding stair climbing no longer has the emphasis formerly placed upon it. If patients live on the second or third floor and walk up slowly, there will probably be no ill effects, provided they do not have active rheumatic fever. A warm climate, such as that of Florida, is not a panacea. The disease in some cases may subside faster in the South, but some of the children sent to Florida from the House of the

*These data were secured from Dr. T. Duckett Jones, Research Assistant, House of the Good Samaritan, Boston, an institution specializing in treatment and research of rheumatic heart disease, and are quoted with his permission.

†This takes into account that some of these patients with only slight heart damage [illegible] who in their twenties or thirties will develop subacute bacterial [illegible] s no means of anticipating in which of these patients the disease

Good Samaritan developed acute exacerbations of the disease while there. Special stress is placed on the importance of a well rounded diet, abundant in vitamins C and D, milk, and on adequate rest and the avoidance of severe fatigue.

As for occupation, with the exception of heavy laborious work there are no special restrictions for patients who have done well and developed little rheumatic heart disease. In other clinics, likewise, it has been observed that many patients have carried on normally in school, play, and in industry several years after a severe initial illness. However, it has been said that the largest proportion of all patients with rheumatic heart disease are left with conditions requiring some limitation of activity. In these cases there will be need for recreational and vocational guidance. For the girls the question of marriage and childbearing requires individualized advice.

During these years there are psychologic aspects which are of the greatest importance. A casual comment, in the child's presence, about heart murmurs or other functional manifestations is likely to arouse anxiety and fear which may result later in cardiac neurosis and excessive introspection. The child should not be labelled a cardiac invalid and allowed to remain one all his life, especially when his condition improves. Some parents, having been given the impression that the child has a fatal illness, are never able to accept the recommendations for increased or normal activity. Continuous conflict between the mother and child, endless anxiety on the mother's part, and lifelong invalidism are common in these cases.

PROBLEMS OF ADULTS

The seriously disintegrating influence on personal and family life and economic loss* to society due to heart disease in adults offer a challenge of the greatest magnitude. Some of the most distressing problems both for the patient and his family arise from prolonged financial or physical dependence on relatives or the community, inability to develop individual capacities or to realize ambitions for self or family, interruption in the continuity of normal pursuits and of usual human relationships, and the constant dread of impending physical disaster.

It has been estimated that over 80 per cent of chronic heart disease is due to syphilis, rheumatic fever, and the hypertensive and vascular diseases.[4] Of primary importance is the need for adequate continuous

*During the study of a group of cardiac patients, it was calculated that $25,235.79 was an approximation of the minimum cost to the community of care for 30 patients. This estimate included only actual hospital, nursing, and convalescent care. Public and private relief were factors in this cost when the patient's cardiac illness caused the family ... many items, such as outpatient care, medication, minor medical ... room, etc., could not be accurately estimated, and were, therefore, ... of earning power was not calculated, but was believed to consti... amount.

medical supervision for an indefinite period of time. The contribution of the social worker in making medical care possible and effective is well recognized. However, many communities still lack appropriate facilities for the care of convalescent patients and those with chronic heart disease.

Of equal importance with medical supervision is the need for regulation of the patient's daily activities. The adjustment of restrictions is influenced by many factors, viz., the personality of the patient, his relationships with the persons in his immediate environment, the conditions in which he works, the general economic situation, and the resources available in the community for the physically handicapped. After the physician and patient together have established the limits of the patient's physical activity, the patient should have a thoughtful interpretation of his condition which will place positive emphasis on his possibilities for attaining some of the satisfactions of life. The social worker and physician should collaborate with the patient in analyzing the patient's interests and needs so that the social worker may have the opportunity for significant constructive service to the patient and his family.

A recommendation for limited activity to a widowed housewife and conscientious mother of three small children, who must subsist on an income of $14 a week, has little likelihood of being carried out without knowledge of her specific duties, her attitude toward their execution, and her ability to delegate some of them to others. The problem of rehabilitation has received some attention in the literature on heart disease, but very little has been said about the problems of the housewife whose income is small. Her multiple activities often require effort more strenuous than that of many men in industry. Washing clothes, scrubbing floors, sweeping, bedmaking, carrying of bundles of food, hauling coal, cooking, etc., comprise a daily routine which cannot be postponed. Too often the patient has no relatives to share these labors or to protect her from the continuous emotional strains incident to the physical care of children, their susceptibility to disease, and the problems of their emotional and intellectual development. When resources within the family are lacking to help the homemaker or to provide a substitute for her, community agencies may furnish assistance or help to place children elsewhere temporarily. The traumatic effect on the emotional development of young, impressionable children of the continuous presence of a case of severe chronic heart disease in the home is not inconsiderable.[5]

The wage earner can occasionally be placed on a less strenuous job within the industry in which he is already employed. When this is not possible, re-education through the state department of rehabilitation is available under certain conditions; in such cases, age, previous

schooling, and adaptability are taken into consideration. The unwillingness of many industrialists to employ the physically handicapped often makes re-employment impossible.

A case[2] in point is that of a well-educated, 52-year-old Swiss hotel steward who had earned approximately $500 a month in fashionable hotels in Europe and America. His first cardiac illness occurred at the age of 47 years, and during the following two years his gradually increasing incapacity made it impossible for him to work and rendered him destitute. After he improved, following total thyroidectomy and social treatment, attempts were made to re-establish him in his former occupation. He was repeatedly refused work because employers feared that such a "poor risk" might increase their rate of workmen's compensation insurance. Although he was prepared to take a position as a "checker" in a restaurant, at a very small salary, he was rejected despite his willingness to sign a waiver of liability. For this patient work was found as a laboratory assistant, but for many others there is no such opportunity.

A fine alternative for many patients is available in communities which maintain workshops for the handicapped. The opportunity to work under sheltered conditions, without the usual industrial competition, to increase gradually the amount of work in proportion to gain in physical capacity, and to earn enough for self-maintenance has been a great boon to patients who might otherwise have become completely dependent and hopelessly invalided. The improvement in the condition of cardiac patients at work in the Project of the Handicapped carried on by the Federal Emergency Relief Administration in Boston justifies the hope that better economic conditions will make possible the establishment of more such projects, either under private or public auspices, with a wage rate which will insure financial independence.

In order to open up opportunities for the development of the patient's personality, appropriate recreation and other interests outside of work deserve more attention than they usually receive. Even if he has opportunities for work and recreation, the patient may not avail himself of them for fear of the adverse effects of the exertion involved. For the social worker, as well as for the physician directing the patient's treatment, an optimistic and encouraging attitude is essential. Experience has demonstrated that some patients, when relieved of undue anxiety, are capable of a life fuller and more effective than they had ever imagined possible.[6, 7] On the other hand, for the patients whose disease is not progressing, the temptation is great to cast aside the precautions for the avoidance of emotional strain and undue physical exertion. Many patients who have done well for years break down later because of unfavorable social influences. This "asymptomatic period"[8] offers the greatest opportunity for preventive work. Many physicians in private practice give this aspect of treatment considerable attention, but in busy clinics and hospitals it is the social worker's function to collaborate with the physician in assisting the patient to prevent or minimize disability. This requires understand-

ing of the patient and his illness, skillful and continuous treatment, and thorough knowledge of, and ingenuity in, the use of community resources.

An appreciation of the role that extreme emotional stress plays in the initial and recurrent attacks of both organic and functional heart disorders is necessary for adequate treatment. Alleviation or elimination of causes of emotional disturbances may increase the patient's activity and his ability to function as a member of society. A recent study[2] disclosed considerable evidence of the close interrelationship of the psychologic, social, and physical factors in patients' reactions to improved health. In some of these patients long continued illness, separation from normal adult activities, physical distress, reaction to dependency on relatives and community, and diminished resources due to the tremendous cost of chronic illness had produced fear and anxiety disabling to a degree out of proportion to the extent of the cardiac illness. Also, improved health in some cases did not reduce the patient's total disability. Within recent years, psychiatric and medical literature[9-15] has revealed an increasing interest in the study of the interrelationships of psychic and somatic factors in cardiac disorders. A greater awareness on the part of social workers of the dynamic aspects of these problems will enable them to recognize what social and emotional factors may be operating, and may help to show that suitable psychiatric and medical assistance is necessary for the reduction of disability and the enrichment of human life.

SUMMARY

Adequate care of patients with heart disease involves a recognition of the significance for etiology, recurrence, and chronicity, of emotional and social influences in the lives of the individual patients. The reaction of the patient to his illness may in certain cases be as important as the disease itself. Therefore, in addition to awareness of the lesion, attention should always be focused on the person with the lesion. A program of care is incomplete that does not give equal attention to the preventive aspects and the therapy. Prerequisites of such a program are regular medical attention for an indefinite period; avoidance of infection, emotional stress, and undue physical activity; adequate nutrition; and a plan of work and recreation suited to the individual's limitations and interests. Schooling and occupational therapy for children in institutions and in their own homes and sheltered workshops and recreational facilities for adults should be fostered by the community. Medical, social, and psychiatric services are required in many cases. These objectives are attainable when there exists a relationship of mutual understanding among physicians, patients, families, social workers, and all others who are trying to diminish the disability in persons ill with heart disease.

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A STUDY OF THE CHEST LEADS OF THE ELECTROCARDIOGRAM WITH AN EVALUATION OF THE POSITIONS OF THE PRECORDIAL ELECTRODE*

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SINCE the introduction of chest leads into clinical electrocardiography in 1932,[1] there has been an increasing number of studies relative to their use and interpretation.[2-12] It is only recently, however, that a standard classification of technique and nomenclature has been established. Specific recommendations have been made that for ordinary purposes Lead IV R or Lead IV F be employed in such a way that relative positivity of the apical electrode is represented in the finished curve by an upward deflection, and relative negativity of the apical electrode by a downward deflection, as is customary with the limb leads.[13]

Many data have been accumulated on the changes in the chest leads in heart disease, especially in cases of infarction of the myocardium and diffuse myocardial damage from coronary disease.[3, 5, 15] Much of the experience in the past has been gained by placing the right arm electrode near the apex and the indifferent electrode on the left leg. This lead is essentially an inverted mirror image of the newly recommended chest leads.[13] By inverting and reversing the old tracing and looking at it in front of a strong light the image will show through the paper and will resemble that of the new chest leads.

Several authors have shown that a shift in the position of the heart may affect the axis deviation.[16, 17, 18, 23, 24] The direction of the extrasystoles caused by stimulating each ventricle may be changed by shifting the chest electrode from left anterior to right anterior thorax or from the left to the right of the spine, posteriorly.[17a] The effect on the electrical axis of rotation of the heart on its longitudinal axis has been demonstrated by Meek and Wilson.[22] In 1930 Wilson[19] showed that it is the electrode near the heart which determines the form of the ventricular electrocardiogram and that it matters little where the second electrode is placed, providing it is sufficiently distant from the heart.[4] Johnston, Kossmann and Wilson[2] also stated that when the distant electrode was placed on the hind leg of a dog, there was, in most of the experiments, a striking resemblance between the precordial curves and curves taken with the exploring electrode placed directly on the heart. More con-

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sistent similarity was found when the indifferent electrode was a central terminal connected through equal resistances to the forelegs and left hind leg. Wood, Bellet, McMillan and Wolferth[3] have pointed out that variations in the character of the tracing can occur if the precordial electrode is allowed to be displaced.

The authors, in a previous study of the significance of absence or small size of the initial positive deflection in the precordial lead,[14] noted that there were often discrepancies in the records of the same patients taken at different times. This was especially frequent in patients with large hearts, and the difficulty seemed probably related to the position of the precordial electrode on the chest. Accordingly, one of us (J. B. V.) thought that it would be of value to check a number of patients with enlarged hearts, using several positions, both inside and outside the apex, for the precordial electrode. Lead IV R was first chosen because we had been using this lead routinely for some months prior to the time when its official adoption was recommended.

In an endeavor to elucidate the variations mentioned above and to evaluate the new precordial leads (IV R, IV F, IV L) recently recommended by the committees of the American and British Heart Associations,[13] multiple precordial leads were made in a series of 67 patients.

METHODS

One of us (J. C. E.) personally studied all of the patients and placed the electrode on the chest after marking and measuring the points of placement. Records were made with a circular electrode, 3 cm. in diameter, from six different positions on the anterior chest wall, employing Leads IV R, IV F, IV L. (Fig. 1).

These positions are designated[13] CR, CF, and CL, according to the lead used (IV R, IV F, or IV L). To illustrate: Lead IV R is taken with the precordial electrode at the right margin of the sternum (CR_1), at the left margin of the sternum (CR_2), midway between the left margin of the sternum and the left midclavicular line (CR_3), at the left midclavicular line (CR_4), at the left anterior axillary line (CR_5), and at the left midaxillary line (CR_6). The subscripts mean that for the sternal leads the precordial electrode has been placed in the fourth intercostal space and that for the other leads it has been placed upon a line drawn from the left sternal margin in the fourth intercostal space to the outer border of the apex beat (or to a point at the junction of the midclavicular line and the fifth intercostal space) and continued around the left side of the chest at the level of the apex beat or of the junction mentioned. (Fig. 1.)

However, in the case of Lead IV R or IV F it has been recommended[13] that the precordial electrode be placed at the outer border of the cardiac apex regardless of the position of the apex with reference to the bony landmarks of the chest. For CF_4 or CR_4, this electrode is placed in the midclavicular line even when the cardiac apex is far to the left of this position. When there is no cardiac enlargement, position CR_4 or CF_4 may be the same as Lead IV R and IV F. In some cases in which there is cardiac enlargement, however, Leads IV R and IV F are the equivalent of CR_5 and CR_6, or CF_5 and CF_6. In taking Lead CR, the left arm wire was connected to the precordial electrode, the right arm wire to the right arm electrode, and the lead switch placed on Lead I, as in taking Lead IV R. In taking Lead CF, the left leg wire was connected to the precordial electrode, the left arm wire to the left leg electrode, and the lead switch was placed on

Lead III, as in Lead IV F. In taking CL, the left leg wire was connected to the precordial electrode, the left arm wire to the left arm electrode, and the lead switch was placed on Lead III as in Lead IV L.*

When the patient under observation was confined to bed, the head of the bed was raised to an angle of 60° to correspond to the angle of the chair used in the heart station for the ambulatory patients. To avoid overshooting, the resistance of the skin was lowered to 2,000 ohms, or less, by careful preparation. In all records the standardization was 1 mv. = 1 cm. In all of the cases studied, the position of the apex was ascertained by the usual clinical methods. If its position could not be located by these means, it was determined by the roentgenogram. Nearly every patient had an orthodiagram or teleoroentgenogram, or both, in order to check the clinical observations. In most instances several electrocardiograms were taken at different times, using multiple precordial leads in each instance. These tracings checked closely with one another except in cases of recent coronary occlusion in which there were the usual changes seen in such serial records.

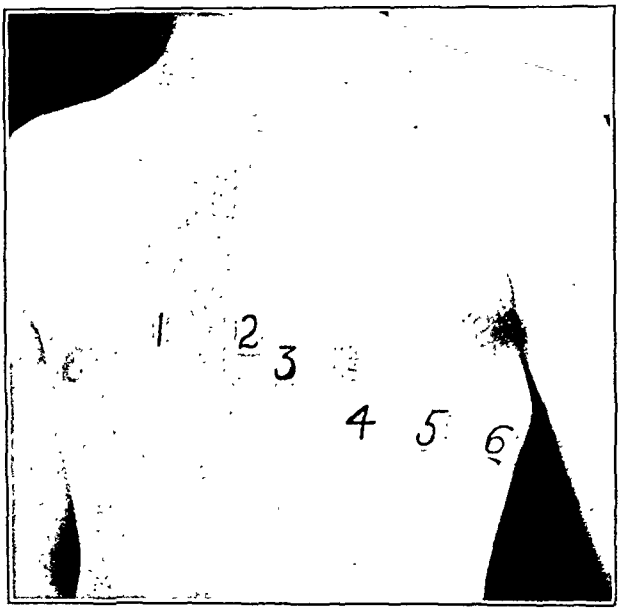

Fig. 1.

Since it had been previously determined[7] that the configuration of the chest in normal boys has no particular correlation to the T-wave pattern in the chest electrocardiogram, as it does in the limb leads, we did not make thoracic measurements in this study.

ANALYSIS OF DATA

The etiological diagnoses in this group of 67 cases are given in Table I. There were 10 subjects with hearts of normal size and function and with no axis deviation (9 adults and 1 child of 13 years). Four patients had no appreciable cardiac enlargement, although some axis deviation was present (left in two cases and right in two cases). Cardiac enlarge-

*It is to be noted that the directions given by the Committees of the American and British Heart Associations for taking Lead IV R say to connect the left leg wire to the precordial electrode, the right arm wire to the right arm electrode, and to place the lead switch on Lead II. Our method of placing the left arm electrode on the precordium and leaving the right arm electrode in place, using Lead I switch, yields exactly the same results and is slightly more convenient, in our opinion.

ment was present in the remaining 53 subjects. Twenty-five patients whose apices lay at the anterior axillary line were studied. Four of these had had myocardial infarction. There were 7 patients who had right axis deviation in the electrocardiogram and moderate cardiac enlargement. Ten patients with coronary thrombosis had moderate cardiac enlargement. The remaining 11 patients had slight or moderate cardiac enlargement as the result of syphilitic aortic regurgitation, hypertension and arteriosclerosis, or chronic rheumatic heart disease.

TABLE I

ETIOLOGICAL DIAGNOSIS

	NUMBER OF CASES
Myocardial infarction	16
Rheumatic heart disease	17
Arteriosclerotic heart disease (7 with hypertension)	16
Congenital heart disease (2 under 12 years of age)	4
Syphilitic heart disease (aortitis)	4
Normal adults (1 child 13 years old)	10
Total	67
The Same Cases Arranged According to the Size of the Heart	
Normal	10
Slight cardiac enlargement (2 with congenital heart disease) (2 with myocardial infarction)	4
Apex at anterior axillary line (4 with myocardial infarction) (6 with right axis deviation)	25
Right axis deviation (Moderate CE*)	7
Myocardial infarction (Moderate CE*)	10
Miscellaneous group (Slight to moderate CE*)	11
Total	67

*Cardiac enlargement.

Normal Subjects.—Each of the 10 normal subjects had a diphasic QRS complex in all positions of the precordial electrode, although in midaxilla the R-wave measured 15 to 25 mm. and the S-wave 0 to 5 mm. The R-wave (initial positive deflection) gradually increased in positivity (height) from the sternum to the left axilla. In none of these cases was there any sudden shift in direction of the QRS complex (Fig. 2). The initial positive deflection (R) varied from 2 to 20 mm. at CR_2 (left border of sternum) and from 2 to 10 mm. at CR_1 (see Table IIA). This agrees with the results of Shipley and Hallaran's study[8] of 21 normal subjects.

Patients With No Cardiac Enlargement.—In 2 patients with old anterior infarction and left axis deviation (but no appreciable cardiac en-

largement), the R-wave was absent at positions C_1, C_2, and C_3 in all three chest leads (CR, CF, and CL). However, in one of these cases R was 22 mm. at C_4, 20 mm. at C_5, and 16 mm. at C_6; in the other, it was absent at C_4, 10 mm. at C_5, and 7 mm. at C_6 (Table III B). Two children without appreciable cardiac enlargement had right axis deviation. One of these had rheumatic heart disease with mitral stenosis, and the other had congenital pulmonic stenosis. In the former, R increased gradually and S decreased as the electrode was moved toward the axilla; in midaxilla the S almost disappeared. In the other case the S was completely lost at

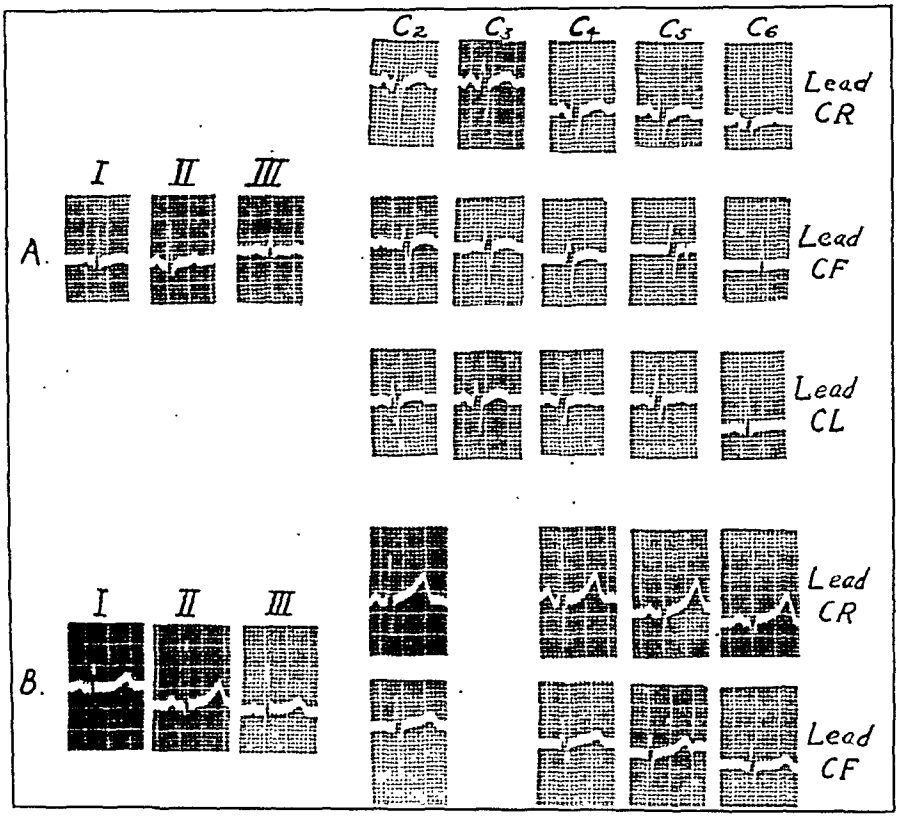

Fig. 2.—Multiple precordial leads of patients with normal hearts.

A, A comparison of Leads CR, CF, and CL in various precordial positions. Position C_1, right edge of sternum 4th intercostal space (not shown because of similarity to C_2). C_2, left edge of sternum 4th intercostal space. C_3, midway between margin of sternum and left midclavicular line. C_4, left midclavicular line at 5th intercostal space. C_5, anterior axillary line. C_6, midaxillary line. Note the greater amplitude of all waves in Lead CR and the gradual change in the QRS complexes with increase in R-waves and decrease in S-waves as the electrode is moved laterally.

B, a comparison of Leads CR and CF, [CL (not shown) nearly identical to CR]. Note the more satisfactory P- and T-waves in Lead CR.

position C_6 (midaxilla). The R-wave was absent in positions 1, 2 and 3 in this case, but appeared in position 4 and was large at C_5 and C_6.

Patients With Cardiac Enlargement.—(1) Apex at anterior axillary line: In 21 cases (excluding 4 cases of myocardial infarction), the apex was located at the anterior axillary line (Table III C). In 14 of these a sudden shift in the direction of the main deflection of the QRS oc-

curred at the midaxillary position (Fig. 3*A*). In nine of these 14 cases there was some gradual decrease in amplitude of the S-waves as the midaxillary position was approached. At this point there was then a sudden shift to a large R-wave without any S-wave. In one case the S-wave and the R-wave gradually increased until, at C_6, there was a

TABLE II

AVERAGE OF QRS AND T DEFLECTIONS IN MILLIMETERS

POSITION	C_1	C_2	C_3	C_4	C_5	C_6	AXIS DEV.
			A				
			10 Normal Subjects				
R	6	10	14	17	18	18	All
S	7	9	9	7	5	2.5	with
T*	+2	+5	+6	+5	+4	+3	none
			B				
			4 Patients With Abnormal Hearts But Without Cardiac Enlargement				
R	R_0Q_6	R_0Q_7	Q_3R_4	11	15	11	Two with old anterior infarctions — Left axis deviation
S	0	0	0	2	1	1	
T	1+	1+	1+	1+	1+	1+	
	1–	1–	1–	1–	1–	1–	
R	15	15	16	21	30	19	Two with pulmonary stenosis — Right axis deviation
S	5	14	10	9	0	0	
T‡	Both +	+	+	+	+	+	
			C				
			21 Patients With Apex at Anterior Axillary Line†				
R	1.5	3	3	6	12	14	11 Left axis deviation
S	7	14	15	15	11	0	6 Right axis deviation
T‡	12+	13+	15+	12+	11+	5+	4 No axis deviation
	9–	8–	6–	9–	10–	16–	
			D				
			5 Patients With Acute Anterior Infarction				
R	R_0Q_{21}	R_0Q_9	0 Q_{11}	0 Q_{12}	0 Q_8	$R_{10}Q_{.6}$	4 Left axis deviation
S	0	0	0	0	0	1	1 No axis deviation
T	4–‡	1+	1+	2+	2+	5–	
	1+	4–	4–	3–	3–		
			E				
			7 Patients With Old Anterior Infarction				
R	0 Q_4	0 Q_8	0 Q_6	$R_0Q_{0.6}$	$R_0Q_{1.4}$	R_8Q_0	5 Left axis deviation
S	3	4	4	6	0	3	2 No axis deviation
T	5+‡	5+	5+	5+	5+	1+	
	2–	2–	2–	2–	2–	6–	

*All T-waves upright in this group; average height given.
†Four with myocardial infarction not included.
‡Number of upright (+) and flat or inverted (–) T-waves.

sudden change to a larger R and absent S. In all of these records the R-wave was over 10 mm. when the S-wave was absent or low in position C_6. In 6 of the 21 cases in which the apex was at the anterior axillary line (in 2 of which right axis deviation was present), there was a gradual decrease in the amplitude of the S-wave until position C_6 was reached, when the S became very small (1 to 3 mm. in height, with an R of 9 to 23 mm.).

In five of these 21 cases the major change in the R/S ratio occurred at the anterior axillary line, with the R and S in the axilla (C_6) of about the same amplitude as at C_5 (Fig. 4A). The S was absent at C_5 in 2 cases, and in 3 there was a small S (2 to 8 mm.) with a large R, the S disappearing at C_6. In only 2 of these 21 cases was there no marked shift in QRS, and in one of these left bundle branch block was present.

In 6 of the 21 cases the R-wave was small, from 1 mm. to 5 mm. in the first five positions, becoming larger in midaxilla. A large S-wave of 10 mm., or over, was present in the first five positions of the precordial electrode. In all of these there was clinical evidence of myocardial damage of severe degree. Only one patient with the apex at the anterior

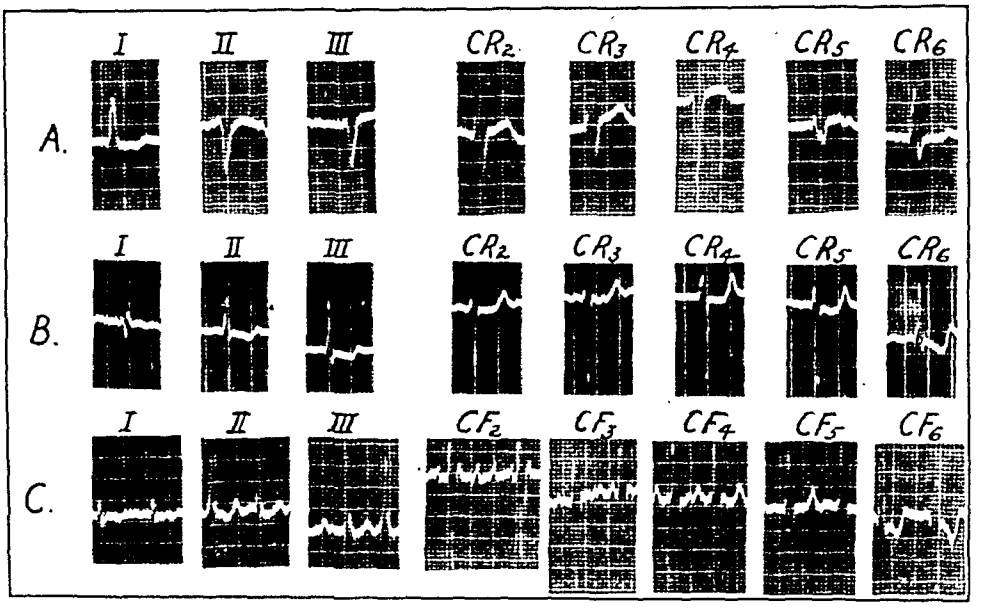

Fig. 3.—Variations in the chest lead with shift of the precordial electrode in patients with the cardiac apex at the anterior axillary line.

A, Case A.P. Hypertensive and arteriosclerotic heart disease. Note the marked change in the QRS complex at positions 5 and 6.

B, Case M.B. Rheumatic heart disease. Observe the striking shift of the ventricular complex at position 6.

C, Case J.L. Rheumatic heart disease; auricular flutter with varying degrees of A-V block. *A similar but less striking shift is seen at C6. This* case also illustrates the value of medial precordial leads in demonstrating the auricular waves when these waves are shown poorly in the limb leads. Lead CR (not shown) was practically identical with lead CF.

axillary line had no R-wave in the first 5 positions. He had an old anterior myocardial infarct, but his precordial electrocardiogram showed an R-wave at C_6.

(2) Apex 2 cm. beyond the midclavicular line: In two cases of cardiac enlargement and left axis deviation there was no great shift, but in one there was a Q-wave of 1 mm. and a diphasic R-S at positions C_1 and C_2 in CR, CF and CL. The T-waves were negative in C_1 and C_2 but upright in C_3, C_4, C_5, and C_6. In one other case in which there

was a tendency to right axis deviation, R increased at the apex, but no S-wave appeared in any of the precordial leads.

Patients With Right Axis Deviation.—There were 13 cases of right axis deviation, and in 7 of these there was a sudden change to a large R and absent S as the electrode was moved from the anterior axillary line to the midaxillary position (six of these seven were cases in which the apex lay at the anterior axillary line and were also included in the study of that group) (Fig. 2*B* and Table III).

TABLE III

AVERAGE OF QRS AND T DEFLECTIONS IN MILLIMETERS

	CR_1	CR_2	CR_3	CR_4	CR_5	CR_6
			A			
			13 Patients With Right Axis Deviation			
R	4	6	7	8	8	13
S	6	14	15	7	8	3
T*	9+	6+	9+	7+	7+	6+
	4–	7–	4–	6–	6–	7–
			B			
			6 Patients With Right Axis Deviation and Apex at Anterior Axillary Line			
R	3	5	5	8	6	12
S	4	11	18	10	14	3
T	–*	1+	3+	3+	3+	1+
	3–	5–	3–	3–	3–	3–
			C			
			7 Patients With Right Axis Deviation and Only Moderate Cardiac Enlargement			
R	5	8	11	15	10	12
S	2	13	11	9	0.6	1
T	3+*	4+	4+	4+	4+	3+
	1–	2–	2–	2–	2–	3–

TABLE IV

J. H., SITUS INVERSUS WITH DEXTROCARDIA

	CR_1	CR_2	C_3	C_4	C_5	C_6
R†	6	3	2	0.5	0.5	0
S	24	23	25	18	15	11
T	+	+	diphasic	diphasic	diphasic	diphasic
R‡	9	7	15	20	23	27
S	27	28	23	13	11	0
T	+	+	+	diphasic	diphasic	diphasic

*Number of upright (+) and flat or inverted (–) T-waves.

†Precordial electrode on left anterior thorax.

‡Precordial electrode on right anterior thorax, with C_1 left sternum, C_2 at right sternum, etc.

In patients with right axis deviation but without appreciable cardiac enlargement, the greatest change occurred at position C_5, where the R became larger and the S smaller. This was much like the changes found in those having hearts of similar size without right axis deviation. In three cases there was a gradual shift as the electrode was moved laterally, and in 3 others there was little change in the character of the QRS in the various positions. One of these last cases was that of a boy of 19

years with the tetralogy of Fallot and marked right axis deviation. One patient with situs inversus and dextrocardia was studied with multiple precordial leads on both the right and left sides of the chest. In this patient the height of the R increased as the precordial electrode was placed in the six corresponding positions on the right chest, but the opposite occurred when the records were made with the electrode in the usual six positions on the left side of the chest. The P-waves were inverted in CF and CR when the chest electrode was on the left anterior thorax but were upright in CL. When the multiple precordial leads were taken on the right side, the P-waves were upright in CF and CR but inverted in CL (Table IV).

Patients With Coronary Thrombosis.—There were 16 patients with old or recent myocardial infarctions on whom multiple precordial

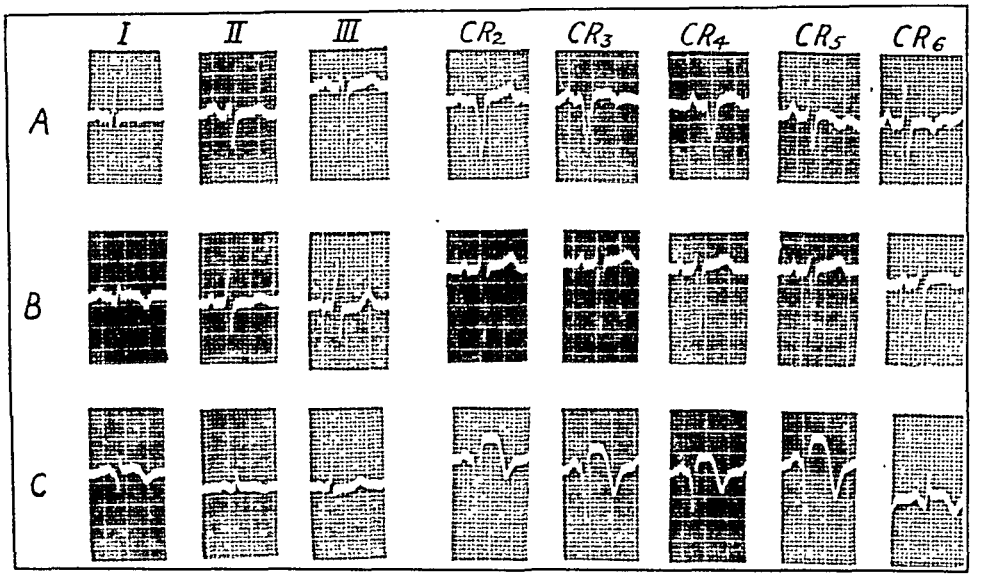

Fig. 4.—Variations in the precordial electrocardiograms of patients with anterior myocardial infarction.

A, Case C.S. Old anterior infarction with marked cardiac enlargement. Note the marked shift in the QRS and T-waves at positions 5 and 6.

B, Case M.F. Old anterior infarction with little cardiac enlargement. This was one of the 2 patients in whom there was no essential change in QRS complex in the various positions.

C, Case E.D. Recent anterior infarction with moderate cardiac enlargement. There is a striking change in the QRS complex at position 6, with loss of the deep Q-wave.

leads were made. Only 2 of these patients had posterior infarctions alone. On 7 who had had recent anterior infarcts serial studies were made; 7 had old anterior infarcts. In 4 of the 14 cases with anterior infarction the cardiac apex was at the anterior axillary line. In these 4 the R-waves were absent in the precordial lead in the positions medial to the apex (Fig. 4*A*). In only one case, however, was the R-wave absent in the midaxillary position (C_6). Five patients had moderate cardiac enlargement, and two of these showed relatively little change in the QRS in any of the six positions. Seven of the 16 patients with

coronary thrombosis had slight or no cardiac enlargement. None of these patients had an R-wave in the first three positions. One began to have an R-wave at the apex, and three lost the initial Q-wave and had the initial positive deflection (R) at midaxilla. Two of these 7 developed the R at the anterior axillary line, having had no R at C_1, C_2, C_3, or C_4. Only one patient had a Q-wave (no initial R) in all positions of the precordial electrode. He had had three previous myocardial infarcts, one anterior and two posterior.

In 8 of the entire 67 cases, the R-wave was absent or small at CR_4, CF_4, and CL_4. It was absent in 5 cases of anterior myocardial infarction and small (2 mm.) in all positions in a case of old myocardial infarction of the anterior type (Fig. 4*B*). The R was small (2 mm.) in one case of myocardial damage in which there was a recent posterior infarct. In one case of recent anterior infarction the R was absent in IV R, IV F, and IV L in all positions of the precordial electrode except C_6, where a 6 mm. R with no S occurred (Fig. 4*C*). The apex was just outside the midclavicular line in this case. In a similar case there was a Q of 2 mm. and an R of 7 mm. in midaxilla, with a larger Q and no R in all other positions. In both of these latter cases the T remained negative (abnormal), and the RST segments were elevated with all positions of the precordial electrode except the midaxillary.

Miscellaneous Group.—In 4 of 11 cases not classified in the previous groups, the apex was from 1 to 2 cm. beyond the midclavicular line. Most of the changes in amplitude of R and S occurred at the midclavicular line (C_4). In the remaining 7 patients, who had myocardial damage, there was a gradual loss of the S-wave with increasing amplitude of the R-wave as the precordial electrode was moved laterally.

A COMPARISON OF LEADS CR, CF, AND CL

In studying the relative merits of the various chest leads, the data from all 67 cases were available. In 7 cases leads CR and CF only were taken, and were essentially the same. In 60 of the patients (10 with normal and 50 with abnormal hearts), leads CR, CF, and CL were taken from the various precordial positions. In 15 of these patients there was no significant difference in the three leads. In 22 cases, however, it was felt that CR was more satisfactory than CF or CL (i.e., it most closely interpreted the clinical picture). In 8 patients CR and CF were similar, and better than CL, the main difference being absent R-waves in several positions, less amplitude of QRS and inverted P-waves in CL.

In only 3 of the 50 patients with abnormal hearts, on whom CR, CF and CL were taken, was CF considered more satisfactory than CR and CL (because of greater amplitude of QRS and T).

In the 12 remaining cases, CR (likewise Lead IV R) seemed more desirable because of the relatively higher amplitude and fewer small R-waves at the midclavicular line in the fifth interspace.

In no instance was CL considered superior to CR or CF.

All of the leads were similar in 4 of the 10 subjects with normal hearts who were used as controls. In 2 the only difference was a greater amplitude of all waves in CR than in CF and CL (Fig. 2). In the other 4 there were flat and diphasic T-waves and inverted P-waves in several positions of Leads CF and CL, but CR was normal.

In 4 cases the QRS did not shift in the midaxillary position with CL, but did with CR and CF. In one case it shifted with CR but not with CF; Lead CL had a diphasic QRS in that position.

In 3 patients, none of whom had myocardial infarction, the R was 2 mm. high in CR_4 but absent in CL_4. With CF the R was absent at C_1 and C_2 in one of these cases, and present at the other positions, where it was similar to CR but of less amplitude.

The Q-waves were deeper in CF and CL than in CR in one patient with anterior and posterior myocardial infarcts. One patient with congenital pulmonary stenosis and little myocardial damage had a 3 mm. Q-wave in CL_6. Another had no shift of QRS in CF_6, but did show it in CR and CL.

In general, Lead CR (likewise Lead IV R) seemed more desirable because it yielded higher amplitude of the QRS complexes. With but few exceptions, the Q-, R-, and S-waves tended to be of greater amplitude in Lead CR than in CF or CL. This factor may be of importance in interpreting the electrocardiograms both of normal persons and those with damaged hearts. For example, a small initial positive deflection (R-wave) is usually regarded as an abnormal finding,[14, 26] but in some of our cases the R-wave was within normal limits (over 2 mm.) in Lead CR and was abnormal (less than 2 mm.) in Lead CF or CL, or both, when taken at the same point on the precordium. Obviously, both results could not be correct, and in most instances of this type Lead CR seemed to be more accurate when correlated with the clinical findings.

There were three deaths among the patients in this series, and a postmortem examination was done in each case. In Case F. D. there was an old infarct at the apex; the heart weighed 635 gm. Clinically, the apex impulse had been in the sixth left intercostal space 3 cm. beyond the midclavicular line. The limb leads showed slight left axis deviation. The precordial leads exhibited a shift from a deep Q-wave and no R-wave in all 5 medial positions to a large R-wave at position C_6 (25 mm. at CR_6, 15 mm. at CL_6, and 14 mm. at CF_6). This type of change is illustrated in Fig. 4C.

This sudden change at position C_6 from an abnormal complex to a normal one was frequently seen in the patients with anterior myocardial infarction. In Case L. M. there was an old thrombosis of the right coronary artery with diffuse scarring of the posterior surface of the left

ventricle. The heart weighed 510 gm. There was right axis deviation with deeply inverted T-waves in Leads II and III. The cardiac apex had been located 2 cm. beyond the midclavicular line in the sixth left intercostal space. The precordial leads had a normal appearance except for negative T-waves at CR_3, CR_5 and CR_6. The shift in the QRS complex occurred at C_5, where the S-wave disappeared, and the R-wave increased in height. This shift at C_5 was commonly found in patients with moderately enlarged hearts and did not represent a significant change in many cases.

In Case C. Sl. the patient had rheumatic heart disease with mitral stenosis. The heart weighed 410 gm. Clinically, the cardiac impulse was located in the sixth left intercostal space 2 cm. beyond the midclavicular line. Roentgenograms revealed cardiac enlargement to the right and left with a large pulmonary conus. The electrocardiograms showed right axis deviation with flat T-waves in the limb leads. The precordial leads had an R- and S-wave in all positions except that S was absent at C_1. The T-waves were all inverted. There was the usual gradual shift of the QRS until, at C_6, the major portion of the QRS complex was above the isoelectric level.

In general, the T-waves were of greater amplitude in Lead CR than in Lead CF or CL. They were usually largest with the electrode at position C_4 in both normal subjects and patients with heart disease. The P-waves were largest and most distinct when the precordial electrode was at position C_2. In some cases the P-waves were more distinct in the precordial lead at position C_2 than in the limb leads. In a few cases, the P-waves were inverted in CF (and IV F) when they were normal in CR and CL (also IV R and IV L).

DISCUSSION

The Normal Lead IV.—In the standard Lead IV[13] the P-wave is upright, and with the precordial electrode at the apex it may be smaller than in the limb leads. If the precordial electrode is moved medially to the left edge of the sternum (fourth intercostal space), the P-wave becomes larger and may exceed that in the limb leads. In certain cases, as in auricular flutter, a lead at this point may be of value in bringing out the auricular waves. However, in this respect only did we find the sternal lead more satisfactory or superior to the precordial leads with the electrode at the apex.

The QRS complex is usually of greater amplitude than in the limb leads, frequently being diphasic, with an R- and S-wave. The R-wave often predominates and may normally be the only wave present. With great amplitude of the R-wave a small Q-wave (1-2 mm.) is seen occasionally and is not of pathologic significance. An R-wave of 2 mm. or less is usually abnormal if the subsequent S-wave is 10 mm. or more

in depth. The significance of absence or small size of the initial positive deflection (R-wave) in the precordial lead has been emphasized by a number of writers, including ourselves.[5, 14, 26]

The T-wave is positive and as a rule sharply peaked, sometimes reaching a height of 10 mm. Very high T-waves in this lead are considered abnormal by some authors, regardless of their direction.[25] The isoelectric R-T segment is of short duration and may occasionally be elevated or depressed slightly (1-2 mm.). Digitalis depresses the R-T segment, as in the limb leads, but frequently to a much greater degree.

As determined by our studies with Leads IV R, IV F, and IV L, there is no characteristic change in the QRS complex associated with either right or left axis deviation or ventricular preponderance, which confirms Willcox and Lovibond's observations[6] with an apex-right arm lead (now known as Lead IV R).

Multiple Precordial Leads.—Our findings agree with those of Sorsky and Wood[7] in so far as the two studies are comparable. Using three positions for the precordial electrode, designated as apex, right, left pectoral (old Lead V—precordial electrode and left leg), they found that within certain limits shift of the exploring electrode to the right of the apex yields a relatively smaller initial positive deflection and a less inverted T-wave. Shift of the exploring electrode to the left tends to have the opposite effect. They found a small Q in the apex-right arm lead in 30 of 150 normal subjects, and its counterpart, a small R, with the old apex-left leg lead, in 20 of 150 normal subjects. On the whole, we agree with the conclusions drawn by Shipley and Hallaran[8] from their study (using three positions of the precordial electrode) of 21 normal persons, that alterations of the simple QRS form are much more frequent in lateral than in medial positions. The more distant the chest electrode is from the heart laterally, regardless of size or axis deviation, the smaller the S becomes and the greater the R/S ratio. The total amplitude of the QRS becomes smaller as the precordial electrode is moved from the apex, whether in a medial or lateral direction. The height of the R-wave increased as the precordial electrode was moved laterally from the sternum in all of our cases except a few with anterior myocardial infarction. Even in some of these an R-wave appeared at C_5 and C_6 (replacing an initial Q-wave), and in two an R appeared at C_4. With left bundle branch block the R-wave may be small or absent, and the RS-T segment elevated in all positions except C_6. There was an abrupt shift in the R/S ratio (large R and small or absent S) at C_5 in most patients with moderately enlarged hearts, and at C_6 in those whose hearts extended to the left anterior axillary line or beyond. All of the normal subjects had some change in the QRS complex in the multiple positions. There were four of the 57 patients with abnormal hearts whose QRS complexes did not change appreciably when the precordial electrode was moved from one position to another. Only

five patients had no initial positive deflection of the QRS at all of the positions, and these were all cases of anterior infarction. Two patients had R-waves of approximately 2 mm. in all positions.

In persons with normal hearts we found, as did Shipley and Hallaran,[8] that the T-wave tends to be largest with the precordial electrode at the apex. In our series the most satisfactory position for recording the T-waves was C_4 (midclavicular line), with the right arm as the indifferent electrode (CR). Hall[21] found this position (Lead IV R) reliable in studying cases of anterior myocardial infarction and noted that the T-waves in this lead were often still negative after the T-waves in Lead I had returned to normal.

The P-waves were largest and most distinct at position C_2 and more satisfactory with Leads CR and CL than CF. Because of variations in the P-waves and a tendency to small initial positive deflections of the QRS at the sternal position, we do not feel that this position is desirable for routine use, although it might occasionally be of value for special studies in conditions such as auricular flutter (Fig. 3*C*).

One case not included in this series was of interest in connection with the various precordial leads. A patient with purulent pneumococcic pericarditis (diagnosis substantiated at autopsy), showed the electrocardiographic pattern typical of acute pericarditis (elevation of the RS-T segments in all of the limb leads). Lead IV R showed a striking elevation of the RS-T segment which persisted on serial examinations. Vander Veer and Norris[27] found no significant abnormalities in Lead V (Wolferth and Wood, apex and left leg) in 4 cases of purulent pericarditis in which there were striking changes in the limb leads. Bellet and McMillan,[28] who studied patients with pericarditis by means of Leads IV, V, and VI (old terminology), found RS-T deviations in all of these leads in some cases, but it was most striking in Leads IV and VI. The logical explanation of this finding (i.e., little or no change in Lead V in pericarditis) is that the algebraic summation of the deviations of the RS-T segments in Leads IV and VI is approximately equal to that of Lead V. Thus, with depression of the RS-T segment in old Lead IV and elevation of the same segment in Lead VI, Lead V would tend to be isoelectric in these cases. For this reason, Lead IV F (the inverted mirror image of old Lead V, and taken at identical points) is inferior to Lead IV R as a diagnostic aid in this condition (Fig. 5).

There are probably several factors which affect the size and contour of the QRS complex in the precordial leads. Analysis of our data suggests that the size of the heart (enlargement) and the position of the precordial electrode are two very important ones. With normal hearts there were only gradual and slight changes in the QRS complex as the precordial electrode was moved laterally. The most striking changes occurred in the patients with enlarged hearts when the precordial electrode was placed on or outside the apex. In several of these, definitely

abnormal precordial electrocardiograms in the medial positions (which interpretations concurred with the clinical picture) became normal when the electrode was placed at or just outside the apex (Fig. 4*A*). This shift of the QRS complex occurred with both right and left axis deviation when the heart was enlarged.

Our studies suggest that ordinarily it is desirable to place the precordial electrode at the *position of the apex* (midclavicular line, fifth left intercostal space) in patients with *normal* or only *slightly enlarged hearts.* However, in patients with *moderately* or *greatly enlarged hearts,* we feel that the electrocardiogram will more often substantiate the clinical diagnosis if the precordial electrode is placed *medial to the apex* (left border of dullness), *and never farther to the left than the anterior*

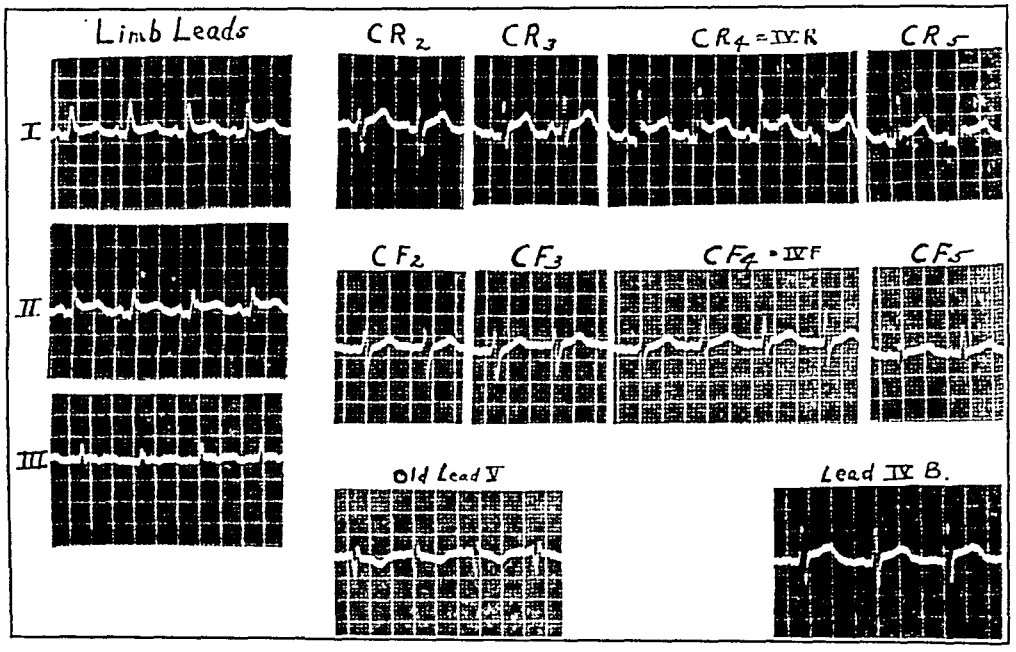

Fig. 5.—Case M.L. White woman 67 years of age. Pneumonia followed by pericarditis. Pericardial tap (350 c.c.) revealed a seropurulent fluid with a few gram-positive cocci and *Staphylococcus aureus* on culture. This record, taken during the acute stage, shows the typical pattern of acute pericarditis in the limb leads. In the precordial leads it is quite evident that Lead CR is superior to Lead CF in demonstrating the acute changes (elevation of the R-T segments). This change is most striking when the electrode is placed at the apex area (CR4 or IV R). Practically no R-T segment change is present in Lead CF at any precordial position. Lead CL in the same positions showed no R-T deviations. Old Lead V and Lead IV B likewise show no change of diagnostic significance.

axillary line. This point of view is not in keeping with the recent recommendations[13] for precordial leads, but we believe that the results will be more satisfactory in cases in which the heart is enlarged if this rule is followed. The whole question of the optimum position of the precordial electrode for routine use is not settled; it is very probable that for best results the cases will have to be individualized and perhaps more than one position utilized in many instances. Certainly, in the study of some pathologic conditions, such as pericarditis and infare-

tion of the lateral wall of the left ventricle, no one lead can give completely satisfactory results, and in cases of this type exploration of several precordial areas is often indicated.

Roth[4] points out that in 1900 Einthoven and de Lint[29] were searching for a lead that would yield the largest possible deflections in the electrocardiogram and came to the conclusion that this requirement was fulfilled best by the right-arm-apex lead now known as Lead IV R. This lead yields maximal auricular and ventricular complexes with the galvanometer string at standard sensitivity. In the majority of instances, in our experience, Lead CR_4 fulfills these conditions better than CF_4 or CL_4. It seems to us that if a single precordial lead is to be taken routinely, Lead CR_4 (midclavicular line, fifth intercostal space, and right arm) is the most desirable.

SUMMARY

1. Multiple precordial leads were studied in 67 persons. Ten of these had normal hearts and the remainder were suffering with cardiac disease of various kinds. The recent recommendations of the American and the British Heart Associations for routine and multiple precordial leads were followed. Leads IV R, IV F and IV L were taken with the precordial electrode just outside the apex and the indifferent electrode on the right arm, left leg, and left arm, respectively. The galvanometer connections were made in such a way that relative positivity of the electrode nearer the heart was represented by an upward deflection (R-wave). The multiple leads, designated CR, CF, and CL, were taken with the precordial electrode in six different positions extending from the right sternal border to the left midaxillary line (C_1, C_2, C_3, etc.). The normal Lead IV and its variations are discussed.

2. In medial positions (near the sternum) the initial positive deflection (R-wave) tends to be small, and the following S-wave large. As the precordial electrode is moved laterally, the size of the R-wave tends to increase and that of the S-wave to decrease. In normal hearts this change in the QRS complexes is slight, but, when the heart is enlarged, the shift of the QRS is often striking, and may be quite sudden and marked with only a slight change in position of the precordial electrode. A complete change of the QRS complexes from abnormal in the medial positions to normal in the axillary positions was seen in several of the patients with diseased, enlarged hearts. This was especially evident in those who had previously had anterior myocardial infarcts. There was no relation of this shift to the electrical axis in the limb leads.

3. The T-waves were usually most satisfactorily recorded with the exploring electrode near the usual apex area (5th intercostal space, left midclavicular line). The P-waves, in most instances, were largest when the electrode was placed in the medial positions, just to the left of the sternum.

4. All waves tended to be of greater amplitude with Lead CR than with Lead CF or CL. The reasons for preferring Lead CR (and IV R) to Lead CF in cases of pericarditis are given.

5. For routine work, when only one precordial lead is taken, we believe that Lead IV R (apex and right arm) is the one of choice, *provided that the heart is not appreciably enlarged.* With *moderate or marked cardiac enlargement,* it seems preferable to place the precordial electrode *medial to the apex* and never farther to the left than the anterior axillary line.

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THE CARDIAC OUTPUT IN COMPENSATION AND DECOMPENSATION IN THE SAME INDIVIDUAL*

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THERE are conflicting reports concerning the level of cardiac output during compensation and decompensation in the same individual. The majority of studies during compensation and decompensation have consisted of two measurements of cardiac output—one during decompensation, the other after improvement. In this study serial determinations of the cardiac output have been made in four patients during various stages of congestive failure. In one patient the output of the heart was measured on two occasions—shortly after the onset of congestive heart failure, and several times following restoration of compensation. In three other patients, who never regained compensation completely, the cardiac output was measured during relative improvement and relapse.

Employing older methods for cardiac output determinations, the accuracy of which when pulmonary congestion is present has been questioned,[1] Meakins and Davies[2] reported increased cardiac outputs after restoration of compensation. In one patient Dautrebande[3] found that the cardiac output decreased as congestive failure appeared. Bansi and Groscurth[4] studied two patients with decompensation, in one of whom the output was larger, and in the other smaller, than normal. Kroetz[5] studied sixteen patients during cardiac decompensation and later during compensation. In this series the average cardiac output during decompensation was 2.08 liters, and after recovery, 3.14 liters. Eppinger, von Papp and Schwarz[6] reported a distinct tendency toward *increased* cardiac output during failure.

With a newer and more reliable method for the measurement of cardiac output during decompensation—the three-sample acetylene method of Grollman—Harrison, Friedman, Clark, and Resnik[7] determined the cardiac output in fifteen patients during, and after recovery from, congestive failure. In only three instances was restoration of compensation associated with an increase of cardiac output. Using their dye-injection method, Kinsman and Moore[8] have found an average increase of 25 per cent in cardiac output following return of compensation in a series of sixteen patients. However, in five of these patients compensation was associated with a slight decrease in cardiac output.

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Our studies in various stages of cardiac failure in the same patients were carried out as follows.

METHOD

All patients were studied under basal conditions. The three-sample acetylene method of Grollman, as modified by Grollman, Friedman, Clark, and Harrison[9] for the measurement of cardiac output in the presence of pulmonary congestion, was employed in all cases. The vital capacity, circulation time, and venous pressure were also determined on the same day. The vital capacity was measured according to the standard established by Blumgart and Weiss.[10] The arm-to-carotid-sinus circulation time was done by the cyanide method of Robb and Weiss.[11] Venous pressure in the cubital vein was determined by the direct method of Moritz and Tabora.[12] Fluoroscopic examination of the heart was made in all cases with especial reference to the amplitude of excursion of the cardiac borders.

RESULTS

The results of the study of the four patients are summarized in the case reports and in the figures and tables.

Comparative studies with the acetylene and direct Fick methods showed close parallelism of results in decompensated patients under basal conditions, although the absolute values were not identical.

We believe, therefore, that the results to be described are significant, but realize that probably no indirect method of measuring cardiac output is accurate to the cubic centimeter.

Case 1, W. P., is of especial interest because of complete restoration of compensation between and following two attacks of congestive failure, and because of the intelligence and cooperation of the patient.

CASE 1.—W. P. *Diagnosis:* Arteriosclerotic and hypertensive heart disease; cardiac hypertrophy and dilatation; congestive heart failure.

A white man, 49 years of age, was admitted to the Cincinnati General Hospital May 26, 1936. The patient complained of slowly increasing dyspnea on exertion for six months and swelling of the ankles for one month. During the two months prior to admission to the hospital he became much worse, with sensations of weakness while driving his automobile and attacks of paroxysmal nocturnal dyspnea. There was no history of substernal pain. Five years earlier he had been told that he had high blood pressure.

Examination revealed a well-developed, well-nourished white man lying flat in bed, not appearing acutely ill. The pupils reacted to light and during accommodation; the retinal arteries were greatly narrowed and compressed the veins which they crossed. The lips were slightly cyanotic. There was some bulging of the chest, posteriorly, at the base. Below the level of the sixth thoracic vertebra the percussion note on the right side was flat, and the intensity of the breath sounds decreased. The heart was generally enlarged. Roentgenographic measurements showed that the shadow of the great vessels was 8 cm. wide at the second rib, and the cardiac shadow 15.5 cm. wide at the fourth rib; the Danzer ratio was 0.62. The rhythm was normal, but the heart sounds were of poor quality. There was a gallop rhythm, and a blowing systolic murmur heard at the apex, transmitted to the left axilla, and diminishing in intensity toward the base. The pulmonic second sound was louder than the aortic second. The blood pressure was 150/120. The liver was not felt, but pitting edema of both ankles was present.

Laboratory Data.—The specific gravity of the urine was 1.010, and a trace of albumin was present. The hemoglobin was 78 per cent, the erythrocyte count 4,100,000, the leucocyte count 7,800, and the differential leucocyte count normal. An electrocardiogram showed left axis deviation; T_1 was inverted, and T_2 and T_3 were isoelectric.

Course.—The usual treatment for cardiac failure was instituted and 700 c.c. of clear fluid were removed from the right chest by thoracentesis. On June 3, 1936, the cardiac output was 3.57 liters per minute, the stroke volume 37 c.c., the vital capacity 2.5 liters, the basal metabolic rate +11, the oxygen consumption 251

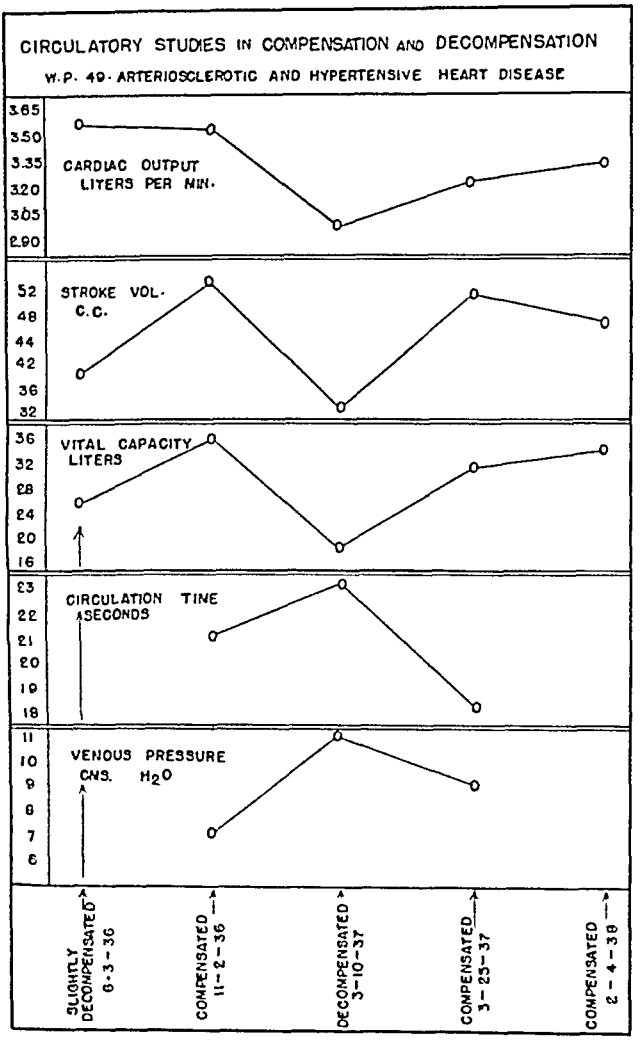

Fig. 1.—Case 1, W. P.

c.c. per minute, and the arteriovenous oxygen difference 70 c.c. per liter. The patient improved sufficiently to be discharged on June 26, 1936. Thereafter he was examined in the Cardiac Clinic at weekly intervals and showed no evidence of congestive failure. Digitalis in doses of 1½ grains daily was continued throughout this period.

On Nov. 2, 1936, when the patient was fully compensated, the cardiac output was 3.56 liters per minute, the stroke volume 52 c.c., the vital capacity 3.5 liters, the circulation time 21 sec., the basal metabolic rate +15, the oxygen consumption 264 c.c. per minute, the arteriovenous oxygen difference 74 c.c. per liter, the venous

pressure 7 cm. of water, and the arterial pressure 164/112. The patient was advised to continue taking digitalis and to return to the Cardiac Clinic at weekly intervals. He did this until Dec. 1, 1936, when he discontinued the digitalis because he was feeling so well. He remained symptom-free for the following three weeks but then began to experience rather severe dyspnea. He resumed digitalis in doses of 1½ grains, but his condition did not improve. The weakness and dyspnea became so marked that he was forced to return to the hospital March 9, 1937.

Examination at this time revealed marked dyspnea but no cyanosis. The neck veins were distended. The heart was enlarged; the apex beat was diffuse and was located in the fifth intercostal space about 11 cm. from the midsternal line.

TABLE I

SUMMARY OF OBSERVATIONS IN CASE 1, W. P.

	ARTERIAL BLOOD PRESSURE (MM.HG)	OXYGEN CONSUMPTION PER MINUTE (C.C.)	CIRCULATION TIME (SEC.)	VITAL CAPACITY (LITERS)	ARTERIOVENOUS OXYGEN DIFFERENCE PER LITER (C.C.)	VENOUS PRESSURE (CM. H_2O)	CARDIAC OUTPUT PER MINUTE (LITERS)	STROKE VOLUME (C.C.)
6/3/36 Slightly decompensated.		251 (B.M.R. +11)		2.5	71.3 69.3		3.57	37
11/2/26 Compensated.	164/112	264 (B.M.R. +15)	21	3.5	75.2	7.0	3.56	52
3/10/37 Decompensated; marked congestion of lungs; dyspnea; feeble cardiac pulsations.	180/140	286 (B.M.R. +20)	23	1.8	94.5 100.0	11.0	2.94	32
3/25/37 Compensated; no evidence of failure; cardiac pulsations more vigorous but still below normal.	160/130	258 (B.M.R. +10)	18	3.1	79.7 81.7	9.0	3.20	50
2/4/38 Compensated; cardiac pulsations full and active.	176/120	288		3.3	85.0 91.0		3.27	45

The teleoroentgenogram disclosed the fact that the size of the cardiopericardial shadow had increased slightly since the previous examination; there was marked congestion of both lungs. The rhythm was normal except for an occasional premature contraction. The heart sounds were of poor quality. There was a high pitched, blowing systolic murmur heard at the apex and transmitted to the axilla. The aortic second sound was louder than the pulmonic second. The blood pressure was 188/140. Numerous râles were heard at the bases of both lungs. The edge of the liver was felt two fingerbreadths below the costal margin and was slightly tender. There was no dependent edema.

Laboratory Data.—The specific gravity of the urine was 1.015; a trace of albumin and acetone and a few hyaline casts were present. The hemoglobin was

15 gm. per cent, the erythrocyte count 5,170,000, the leucocyte count 9,850, and the differential leucocyte count normal. The blood Kahn reaction was negative. The urea nitrogen content of the blood was 15 mg. per cent.

On March 10, 1937, after the usual treatment, the cardiac output was 2.94 liters per minute, the stroke volume 32 c.c., the arteriovenous oxygen difference 97 c.c. per liter, the vital capacity 1.8 liters, the circulation time 23 sec., the basal metabolic rate +20, the oxygen consumption 286 c.c. per minute, and the venous pressure 11 cm. of water. Fluoroscopic examination revealed feeble cardiac pulsations.

After completion of the above studies 2 c.c. of mercupurin were administered intravenously, which resulted promptly in a diuresis of 3000 c.c. Three days later the bases of the lungs were free of congestion, the liver could not be felt, the dyspnea was greatly diminished, and the arterial pressure was 154/120.

On March 25, 1937, when compensation was fully restored, the cardiac output was 3.20 liters per minute, the stroke volume 50 c.c., the arteriovenous oxygen difference 80.7 c.c. per liter, the vital capacity 3.1 liters, the circulation time 18 sec., the basal metabolic rate +10, the oxygen consumption 258 c.c. per minute, and the venous pressure 9 cm. of water.

The patient was discharged March 26, 1937, and advised to continue taking 1½ grains of digitalis daily. Since that time he has returned regularly to the Cardiac Clinic and has had no signs or symptoms of decompensation.

On Feb. 4, 1938, when the patient was symptom-free and actively engaged in his occupation as a salesman, the cardiac output was 3.27 liters per minute, the stroke volume 45 c.c., the arteriovenous oxygen difference 88 c.c. per liter, the vital capacity 3.3 liters, the basal metabolic rate +24, the oxygen consumption 288 c.c. per minute, and the arterial pressure 176/120. Fluoroscopic examination showed active cardiac pulsations.

CASE 2.—J. H. *Diagnosis:* Syphilitic heart disease; aortic insufficiency; congestive heart failure.

A 39-year-old colored man was admitted to the Cincinnati General Hospital May 17, 1937, complaining of shortness of breath and swelling of the abdomen and ankles for the preceding six months. During the five months prior to admission to the hospital he had become progressively worse, with severe attacks of paroxysmal nocturnal dyspnea associated with severe cough which was productive of frothy and frequently blood-tinged sputum. The edema at first involved only the ankles, but gradually spread upward to the legs, thighs, and abdomen. The patient was confined to bed for four months prior to admission to the hospital. He had been told three months earlier that he had "a leak of the heart and bad blood." There was no history of previous cardiac failure.

Examination revealed a well-developed, well-nourished colored man, lying in semi-Fowler's position, appearing acutely ill, suffering from marked dyspnea and orthopnea, and occasionally coughing up frothy, blood-tinged sputum. There was marked edema of the lower extremities and of the trunk to the level of the umbilicus. The neck veins were distended. The pupils reacted to light and during accommodation. The retinal arteries showed moderate tortuosity and narrowing. No cyanosis was present. The respirations were rapid and shallow. There were numerous moist râles in both lungs extending to the angles of the scapulae, with signs of fluid at the right base. The heart was enlarged to the left. The diffuse apex impulse was felt in the sixth intercostal space 11 cm. from the midsternal line. Retrosternal dullness was 7 cm.; relative cardiac dullness 4 by 15 cm. The rhythm was normal. There was a marked gallop rhythm at the apex, and soft blowing systolic and diastolic murmurs were heard at the base. The blood pressure was 145/45. The pulse was of the Corrigan type and Duroziez's sign was present. The edge of the liver was felt three fingerbreadths below the costal margin, and there

was shifting dullness in the flanks. There was marked pitting edema from the costal margins downward. The reflexes were all present and active.

Laboratory Data.—The urine contained a moderate amount of albumin (++); its specific gravity was 1.025. The hemoglobin was 12 gm. per cent, the erythrocyte count 4,200,000, the leucocyte count 9,600, and the differential leucocyte count normal. The blood Kahn reaction was positive (+++). The urea nitrogen content of the blood was 20 mg. per cent. The electrocardiogram showed left axis deviation; T_1 and T_2 were isoelectric, and T_3 diphasic.

Course.—The patient was given a Karell diet and digitalized. Two days later, May 19, 1937, the cardiac output was 1.75 liters per minute, the stroke volume 16 c.c., the arteriovenous oxygen difference 136.5 c.c. per liter, the vital capacity

TABLE II

SUMMARY OF OBSERVATIONS IN CASE 2, J. H.

	ARTERIAL BLOOD PRESSURE (MM. HG)	OXYGEN CONSUMPTION PER MINUTE (C.C.)	CIRCULATION TIME (SEC.)	VITAL CAPACITY (LITERS)	ARTERIOVENOUS OXYGEN DIFFERENCE PER LITER (C.C.)	VENOUS PRESSURE (CM. H_2O)	CARDIAC OUTPUT PER MINUTE (LITERS)	STROKE VOLUME (C.C.)
5/19/37 Decompensated 4+; edema 3+.	150/40	240 (B.M.R. +14)	43	1.22	136.2 137.5	14.5	1.75	16.0
5/20/37 Condition unchanged.	150/50	248 (B.M.R. +18)		1.38	137.0 135.5		1.81	15.3
5/21/37 Considerably improved; some edema; dyspnea.	145/30	232 (B.M.R. +10)	35	1.82	116.2 110.2	5.0	2.10	18.4
6/3/37 No edema; dyspnea on slight effort; failure at bed rest occurred 3 days later.	110/50	202 (B.M.R. −3)	33	1.90	121.0 88.5	5.0	1.98	18.0

1.22 liters, the circulation time 43 sec., the basal metabolic rate +14, the oxygen consumption 240 c.c. per minute, and the venous pressure 14.5 cm. of water.

On the next day, May 20, 1937, the cardiac output was 1.81 liters per minute, the stroke volume 15.3 c.c., the arteriovenous oxygen difference 135.0 c.c. per liter, the vital capacity 1.38 liters, the basal metabolic rate +18, and the oxygen consumption 248 c.c. per minute.

The patient was given 2 c.c. of mercupurin intravenously, which was followed by a prompt diuresis of 6.5 liters with a twenty-four pound loss of weight in twenty-four hours. On May 21, 1937, there were a few râles at the base of the right lung, a protodiastolic gallop rhythm at the apex, and to-and-fro murmurs at the base of the heart. There was much less peripheral edema. On this day the cardiac output was 2.10 liters per minute, the stroke volume 18.4 c.c., the arteriovenous oxygen difference 113.0 c.c. per liter, the vital capacity 1.82 liters, the circulation time 35 sec., the basal metabolic rate +10, the oxygen consumption 232 c.c. per minute, and the venous pressure 5 cm. of water.

The patient continued to improve steadily, and on June 3, 1937, the lungs showed no abnormalities, and the peripheral edema had disappeared. However, gallop rhythm persisted, and there was marked dyspnea on the slightest exertion. On this day the cardiac output was 1.98 liters per minute, the stroke volume 18.0 c.c., the arteriovenous oxygen difference 105.0 c.c. per liter, the vital capacity 1.9 liters, the circulation time 33 sec., the basal metabolic rate −3, the oxygen consumption 202 c.c. per minute, and the venous pressure 5 cm. of water.

Five days later the patient began to have a daily fever (101° to 103° F.), and at absolute bed rest developed frank congestive failure with a return of all

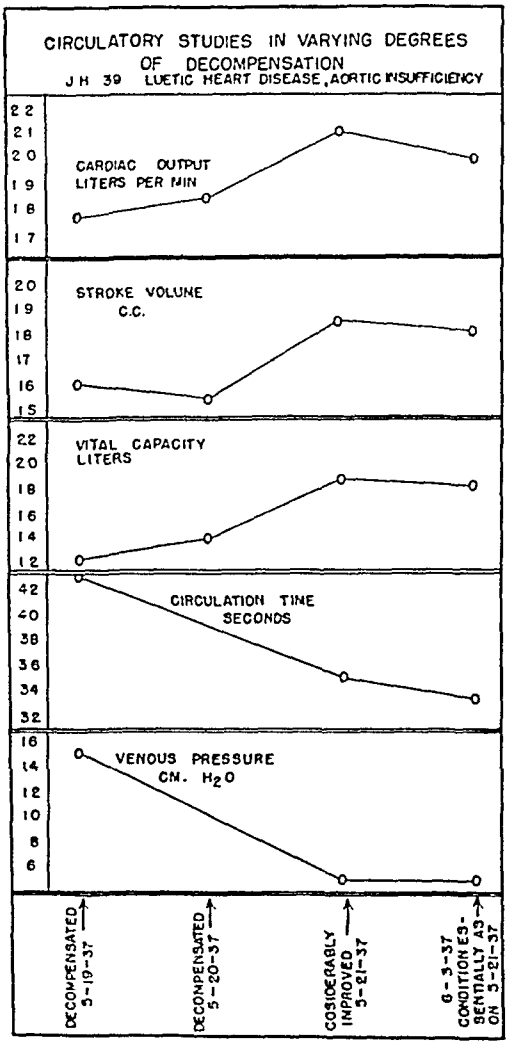

Fig. 2.—Case 2, J. H.

his previous symptoms. However, with the usual therapy, he improved sufficiently to be discharged June 17, 1937. Two months later the patient returned to the hospital and died with congestive heart failure.

Case 3.—M. B. *Diagnosis:* Arteriosclerotic and hypertensive heart disease; congestive heart failure.

A white woman, 76 years old, was admitted to the Cincinnati General Hospital March 18, 1936, complaining that she had been short of breath for one year and had had swelling of the ankles for three months. Two weeks prior to admission

she began to have frequent and rather severe attacks of paroxysmal nocturnal dyspnea associated with a sensation of strangling. At that time she observed an increase in the edema of her legs and noted that the abdomen was increasing in size. These symptoms became progressively worse. The patient had been told about one year before that she had high blood pressure.

Examination revealed an obese white woman, sitting up in bed, with rather marked dyspnea. There was slight cyanosis of the lips and nail beds. The neck veins were distended. The pupils were irregular and reacted sluggishly to light and during accommodation. Examination of the fundi showed moderate tortuosity of the retinal arteries and compression of the veins which they crossed. The chest was barrel-shaped and the percussion note was slightly impaired at the base of the right lung. There were numerous moist râles at the bases of both lungs. The heart showed general enlargement. Teleoroentgenographic measurements were retrosternal dullness 7.5 cm. at the second rib, 13 cm. at the fourth rib. The greatest cardiac diameter was 18.5 cm. There was marked widening of the aortic arch

TABLE III

SUMMARY OF OBSERVATIONS IN CASE 3, M. B.

	ARTERIAL BLOOD PRESSURE (MM.HG)	OXYGEN CONSUMPTION PER MINUTE (C.C.)	VITAL CAPACITY (LITERS)	ARTERIOVENOUS OXYGEN DIFFERENCE PER LITER (C.C.)	VENOUS PRESSURE (CM. H_2O)	CARDIAC OUTPUT PER MINUTE (LITERS)	STROKE VOLUME (C.C.)
4/28/36 Slightly decompensated.	190/100	221 (B.M.R. +20)	1.58	77.0 87.0	20	3.08	55
2/12/37 Severely decompensated; very dyspneic.	140/100	248	0.85	95.5 93.5	16	2.62	30
2/13/37 Condition unchanged.	155/90	260	0.80	104.0 92.0		2.72	32

and calcification of the aorta. There was also accentuation of the pulmonary conus with enlargement of the right ventricle. The rhythm was normal. There was a blowing systolic murmur heard over the aortic and mitral areas. The blood pressure was 185/120. The tender liver edge was felt three fingerbreadths below the right costal margin. Free fluid was present in the abdominal cavity. There was marked edema of the lower extremities.

Laboratory Data.—The specific gravity of the urine was 1.015, and it contained a trace of albumin. The hemoglobin was 80 per cent, the erythrocyte count 4,400,000, the leucocyte count 8,500, and the differential leucocyte count normal. The blood Wassermann reaction was negative. The urea nitrogen content of the blood was 32 mg. per cent, and the carbon dioxide combining power 61 volumes per cent. The electrocardiogram showed nodal rhythm of type II and left axis deviation; T_1 was inverted, and T_2 and T_3 were diphasic.

Course.—The usual treatment was instituted. After one month of absolute bed rest patient showed slight improvement, but compensation was not restored.

On April 28, 1936, the cardiac output was 3.08 liters per minute, the stroke volume 55 c.c., the venous pressure of 20 cm. of water, the arteriovenous oxygen difference 82 c.c. per liter, the vital capacity 1.6 liters, the basal metabolic rate

+20? (exact estimation of body surface area impossible because of edema), the oxygen consumption 221 c.c. per minute, and the arterial pressure 190/100.

Sixteen days later the patient had improved sufficiently to be discharged from the hospital. She was advised to continue taking digitalis and to return to the Cardiac Clinic, but she did not follow these instructions.

On October 27, 1936, she was readmitted to the hospital with frank congestive failure. After four weeks of hospitalization the edema disappeared, but effort dyspnea persisted. On Nov. 24, 1936, she was discharged from the hospital but advised to remain in bed at her home.

Six weeks later, following an acute upper respiratory infection, the patient again developed congestive heart failure, and was readmitted to the hospital Feb. 11, 1937.

Examination at this time revealed massive edema of the extremities and abdomen. There were marked dyspnea and orthopnea, distention, and pulsation of

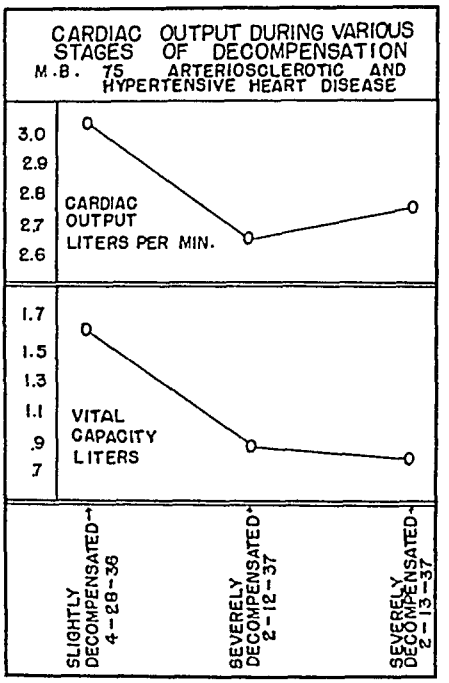

Fig. 3.—Case 3, M. B.

the cervical veins. There were numerous moist râles at the bases of the lungs and signs of small amounts of free fluid in both pleural cavities. The edge of the liver was palpable four fingerbreadths below the right costal margin. The blood pressure was 140/100.

On Feb. 12, 1937, the cardiac output was 2.62 liters per minute, the stroke volume 30 c.c., the venous pressure 16 cm. of water, the arteriovenous oxygen difference 94.5 c.c. per liter, the vital capacity 0.85 liters, and the oxygen consumption 248 c.c. per minute.

The patient was given 2 c.c. of mercupurin intravenously. This was followed by a diuresis of 2,600 c.c. in five hours, with no change in the dyspnea or appreciable effect on the peripheral edema.

Twenty-four hours later the cardiac output was 2.72 liters per minute, the stroke volume 32 c.c., the arteriovenous oxygen difference 98.0 c.c. per liter, the vital capacity 0.80 liters, the oxygen consumption 260 c.c. per minute, and the arterial pressure 155/90.

The patient became progressively worse, and developed intense cyanosis of the lips and nail beds. The edema of the lower extremities, ascites, and hydrothorax remained practically unchanged in spite of a fairly good mercupurin diuresis. Death occurred Feb. 17, 1937.

The anatomical diagnosis was: Generalized arteriosclerosis; cardiac hypertrophy and dilatation, especially right-sided; chronic passive congestion of the viscera; chronic pulmonary emphysema, and arterial nephrosclerosis.

CASE 4.—M. H. *Diagnosis:* Syphilitic and arteriosclerotic heart disease; aortitis with aortic insufficiency and relative mitral insufficiency; congestive heart failure.

A colored man, 41 years old, was admitted to the Cincinnati General Hospital March 2, 1937. He complained of slowly increasing dyspnea on exertion for the preceding year and swelling of the ankles for five months. During the five months prior to admission these symptoms became progressively worse, and were

TABLE IV

SUMMARY OF OBSERVATIONS IN CASE 4, M. H.

	ARTERIAL BLOOD PRESSURE (MM. HG)	OXYGEN CONSUMPTION PER MINUTE (C.C.)	CIRCULATION TIME (SEC.)	VITAL CAPACITY (LITERS)	ARTERIOVENOUS OXYGEN DIFFERENCE PER LITER (C.C.)	VENOUS PRESSURE (CM. H_2O)	CARDIAC OUTPUT PER MINUTE (LITERS)	STROKE VOLUME (C.C.)
3/4/37 Decompensated. Pulmonary and peripheral edema +++, orthopnea.	210/68	435 (B.M.R. +59)		2.3	81.5 86.4	10.0	5.19	51
3/24/37 Discharged. Few rales; no peripheral edema.	150/35	258 (B.M.R. −6)	23	3.7	67.0 74.0	2.5	3.67	46
6/4/37 Decompensated. Edema ++.	170/70	324 (B.M.R. +19)	30	3.1	87.0 85.5	5.0	3.76	38

accompanied by coughing, the expectoration of blood-tinged sputum, and severe attacks of paroxysmal nocturnal dyspnea. Six months prior to admission he was told that he had "high blood pressure and a leaking heart."

The patient had been in the hospital seven years before, when a thyroidectomy was performed for relief of obstructive symptoms in the larynx. He made an uneventful recovery. There was the history of a chancre in 1926, after which he received "shots" twice a week for three months.

The patient was a well-developed and well-nourished colored man suffering from severe dyspnea and orthopnea. Frequent short periods of apnea accompanied by loss of consciousness and dropping of the head were noted. There was moderate distention of the neck veins. The pupils were small, regular, and reacted sluggishly to light and during accommodation. The retinal arteries were narrowed and tortuous and compressed the veins which they crossed; the discs were normal. The percussion note was impaired at the bases of both lungs, where numerous râles were heard. The heart showed general enlargement with diffuse heaving precordial pulsations. The apex beat was diffuse and located in the fifth and sixth intercostal spaces 11 cm. from the midsternal line. The retrosternal dullness was 5 cm., relative

cardiac dullness 3 x 11 cm. The rhythm was normal. High pitched systolic and diastolic murmurs were heard in the third left intercostal space. The blood pressure was 200/70. All of the accessible peripheral vessels were thickened and sclerotic. The arterial pulse was of the Corrigan type. The abdomen was distended, with shifting dullness in the flanks and a definite fluid wave. The edge of the liver was not felt. The lower extremities showed marked pitting edema extending up to the knees. All of the reflexes were present and active.

Laboratory Data.—The specific gravity of the urine was 1.025, and it contained a little albumin (+). The hemoglobin was 13.5 gm. per cent, the erythrocyte count 4,250,000, the leucocyte count 7,700, and the differential leucocyte count

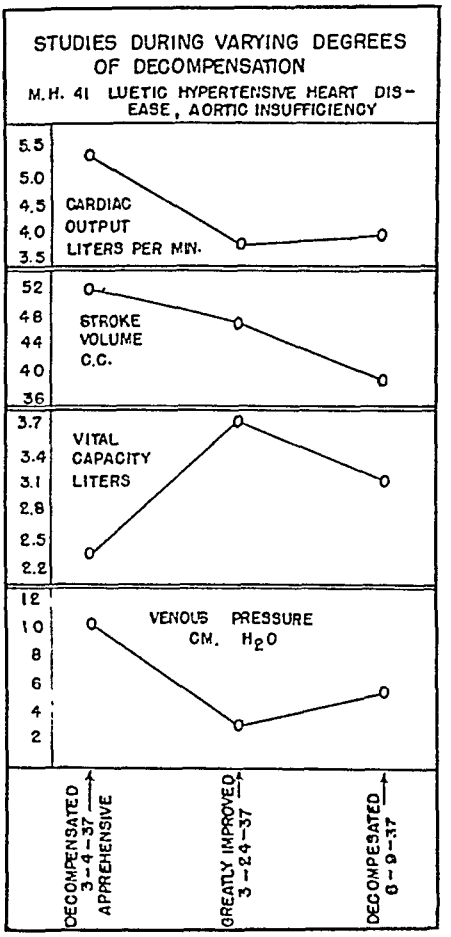

Fig. 4.—Case 4, M. H.

normal. The blood Wassermann reaction (cholesterinized antigen) was rather strongly positive (+++). The phenolsulphonephthalein excretion was 55 per cent in two hours. The electrocardiogram showed left axis deviation, a P-R interval of 0.26 sec., slurring of QRS in Leads I, II, and III, and inversion of T_3.

Course.—The patient was given a Karell diet and digitalized. Two days later, March 3, 1937, the cardiac output was 5.19 liters per minute, the stroke volume 51 c.c., the venous pressure 10 cm. of water, the arteriovenous oxygen difference 83.9 c.c. per liter, the vital capacity 2.3 liters, the basal metabolic rate +59 (patient very apprehensive), the oxygen consumption 435 c.c. per minute, and the arterial pressure 210/68 (patient's weight was 200 pounds; surface area 2.08 square meters).

During the next twenty days the patient improved sufficiently to be discharged from the hospital, at which time the cardiac output was 3.67 liters per minute, the stroke volume 46 c.c., the arteriovenous oxygen difference 70.5 c.c. per liter, the venous pressure 2.5 cm. of water, the vital capacity 3.7 liters, the circulation time 23 sec., the basal metabolic rate −6, and the oxygen consumption 258 c.c. per minute.

The patient was advised to return to the Cardiac Clinic at weekly intervals. During the next two months he was ambulatory, but it was necessary to give him mercupurin twice a week to keep him free of edema.

On June 2, 1937, the patient was readmitted because of congestive failure. There was soft edema of the lower extremities, numerous râles were audible at the bases of both lungs, and the liver was tender and extended three fingerbreadths below the costal margin. There was marked dyspnea on the slightest exertion. The patient was given the usual treatment for heart failure, and two days later, June 4, 1937, the cardiac output was 3.76 liters per minute, the stroke volume 38 c.c., the venous pressure 5 cm. of water, the arteriovenous oxygen difference 86.2 c.c. per liter, the vital capacity 3.1 liters, the circulation time 30 sec., the basal metabolic rate +19, the oxygen consumption 324 c.c. per minute and the arterial pressure 170/70.

The response to treatment was dramatic, and the patient was discharged from the hospital nine days later.

DISCUSSION

In three of the four patients studied, it was found that the more severe the decompensation the lower the cardiac output. In a fourth patient the more severe the failure, the higher the cardiac output.

In a previous report concerning the relationship between cardiac output and cardiac failure,[13] we found that nineteen of twenty patients with congestive failure had subnormal cardiac outputs. Harrison has observed normal, or slightly higher than normal, cardiac outputs not infrequently in decompensated patients, and Kinsman and Moore have occasionally observed normal or supernormal cardiac outputs in the presence of cardiac failure. Thus a subnormal cardiac output is usually, but not invariably, present in cardiac decompensation.

An obvious explanation for the apparent paradox that certain decompensated hearts may maintain a normal output is apparent if one remembers that certain conditions known to increase cardiac output[14] are frequently present in congestive failure, as recently emphasized by Altschule.[15]

1. Exercise (associated with hyperpnea)
2. Increased metabolism
3. Increased venous pressure
4. Long standing anoxemia of tissues
5. Low grade fever
6. Anxiety and apprehension

It is our opinion that the majority of patients with heart failure are not studied under truly basal conditions even though they are con-

tinuously in bed and have fasted for twelve hours. Therefore, it is surprising that the majority of decompensated patients have such low cardiac outputs; the fact that they do suggests a relative inability on the part of the decompensated heart to increase its output in a normal manner.[16]

SUMMARY AND CONCLUSIONS

Repeated determinations of cardiac output have been made in four patients during varying degrees of cardiac decompensation.

In one patient the cardiac output decreased with the onset of congestive heart failure and rose after restoration of compensation.

In two patients, the more severe the decompensation, the lower the cardiac output.

In the fourth patient, the more severe the decompensation, the higher the cardiac output. A theoretical explanation for the apparent paradox has been advanced.

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During the next twenty days the patient improved sufficiently to be discharged from the hospital, at which time the cardiac output was 3.67 liters per minute, the stroke volume 46 c.c., the arteriovenous oxygen difference 70.5 c.c. per liter, the venous pressure 2.5 cm. of water, the vital capacity 3.7 liters, the circulation time 23 sec., the basal metabolic rate −6, and the oxygen consumption 258 c.c. per minute.

The patient was advised to return to the Cardiac Clinic at weekly intervals. During the next two months he was ambulatory, but it was necessary to give him mercupurin twice a week to keep him free of edema.

On June 2, 1937, the patient was readmitted because of congestive failure. There was soft edema of the lower extremities, numerous râles were audible at the bases of both lungs, and the liver was tender and extended three fingerbreadths below the costal margin. There was marked dyspnea on the slightest exertion. The patient was given the usual treatment for heart failure, and two days later, June 4, 1937, the cardiac output was 3.76 liters per minute, the stroke volume 38 c.c., the venous pressure 5 cm. of water, the arteriovenous oxygen difference 86.2 c.c. per liter, the vital capacity 3.1 liters, the circulation time 30 sec., the basal metabolic rate +19, the oxygen consumption 324 c.c. per minute and the arterial pressure 170/70.

The response to treatment was dramatic, and the patient was discharged from the hospital nine days later.

DISCUSSION

In three of the four patients studied, it was found that the more severe the decompensation the lower the cardiac output. In a fourth patient the more severe the failure, the higher the cardiac output.

In a previous report concerning the relationship between cardiac output and cardiac failure,[13] we found that nineteen of twenty patients with congestive failure had subnormal cardiac outputs. Harrison has observed normal, or slightly higher than normal, cardiac outputs not infrequently in decompensated patients, and Kinsman and Moore have occasionally observed normal or supernormal cardiac outputs in the presence of cardiac failure. Thus a subnormal cardiac output is usually, but not invariably, present in cardiac decompensation.

An obvious explanation for the apparent paradox that certain decompensated hearts may maintain a normal output is apparent if one remembers that certain conditions known to increase cardiac output[14] are frequently present in congestive failure, as recently emphasized by Altschule.[15]

1. Exercise (associated with hyperpnea)
2. Increased metabolism
3. Increased venous pressure
4. Long standing anoxemia of tissues
5. Low grade fever
6. Anxiety and apprehension

It is our opinion that the majority of patients with heart failure are not studied under truly basal conditions even though they are con-

tinuously in bed and have fasted for twelve hours. Therefore, it is surprising that the majority of decompensated patients have such low cardiac outputs; the fact that they do suggests a relative inability on the part of the decompensated heart to increase its output in a normal manner.[16]

SUMMARY AND CONCLUSIONS

Repeated determinations of cardiac output have been made in four patients during varying degrees of cardiac decompensation.

In one patient the cardiac output decreased with the onset of congestive heart failure and rose after restoration of compensation.

In two patients, the more severe the decompensation, the lower the cardiac output.

In the fourth patient, the more severe the decompensation, the higher the cardiac output. A theoretical explanation for the apparent paradox has been advanced.

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THE EFFECTS OF THE INTRAVENOUS ADMINISTRATION OF DIGITALIS BODIES ON PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION*

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THE purpose of this study was to determine the effects of digitalis bodies on patients with auriculoventricular dissociation subject to transient seizures of ventricular fibrillation. Since digitalis bodies have been found useful in abolishing both single and multiple premature beats of the ventricles[1, 2, 3] in certain forms of cardiac diseases, it was felt that they might be of value in preventing and abolishing the various ventricular irregularities that precede the paroxysms of ventricular fibrillation in patients with either the transient or established forms of auriculoventricular dissociation.

METHOD OF STUDY

One patient with transient auriculoventricular dissociation and two patients with established auriculoventricular dissociation form the subjects of this study. One of these patients showed generalized anasarca and signs of advanced congestive heart failure at the time of the experiment. The other two were free from such signs. The natural course of the development of their attacks and the successive changes in the rhythm of their hearts were studied carefully over a period of several years.[4, 5, 6] During this entire period they were in the Montefiore Hospital, and hundreds of observations made on their heart rhythms were correlated with electrocardiograms.

These experiments were carried out at a time when it was certain that the patients had not had any changes in their cardiac mechanism for at least forty-eight hours. It was definitely determined from study of both the heart and pulse rates, while the patients were connected to the electrocardiographic circuit, that the basic ventricular rate was fairly constant prior to the onset of the experiments, i. e., that it did not vary more than five beats per minute. When the basic rhythm was interrupted spontaneously by premature ventricular beats, the number of such extrasystoles was counted each minute for at least ten minutes prior to the use of any form of digitalis. The patients were kept in bed constantly, and no drug other than a digitalis body was administered to them throughout the entire period of these studies.

On several occasions, frequently before the drug was used, the effects of the intravenous injection of 1 c.c. of either distilled water or physiologic salt solution were determined in order to rule out any abnormal changes in the rhythm of the heart or in the complexes of the electrocardiograms that might follow the injection of the fluid itself.

One of us timed the clinical manifestations following the injection of the drugs, while the other recorded the time intervals at which changes appeared in the electrocardiograms. All studies were carried out with Lead II only. Successive changes in the rhythm of the heart were recorded as frequently as was thought

*From the Medical Division of the Montefiore Hospital, Service of Dr. Leopold Lichtwitz.
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necessary, and the movement of the galvanometer string was followed for several hours after the use of the drug unless the condition of the patient made this impossible, in which case reliance was placed upon the clinical manifestations.

Digifolin and ouabain were the drugs used. The minimum dose capable of producing transient changes in the rhythm of the heart was arrived at by the method of trial and error. Starting with very minute quantities, the dose was gradually increased until an effect was produced. The amount finally used was based on the average amount required to give a specific effect.

Although observations were repeated on numerous occasions on the same patient, we have thought it advisable to describe only some of the typical protocols. Each of them demonstrates some mode of action of the drugs to which we direct particular attention. Before mentioning these effects, however, it is important to call attention to the successive changes in the cardiac mechanism which take place when ventricular fibrillation develops spontaneously in patients with either transient or permanent auriculoventricular dissociation, so that comparisons may be made with alterations in the rhythm of the heart that might be caused by the drug.

THE ALTERATIONS IN THE RHYTHM OF THE HEART PRECEDING TRANSIENT PERIODS OF VENTRICULAR FIBRILLATION

Transient ventricular fibrillation may appear spontaneously in patients who exhibit normally a sinus rhythm. The preliminary disturbances that usher in the fibrillatory process in such patients are of two types. One of these is a para-arrhythmia in which the sinus rhythm is interrupted by impulses originating in another center. It may continue for several hours, and may accelerate the heart rate greatly before the basic mechanism is disrupted by short runs of ventricular fibrillation that herald a major seizure.[4, 5] In a second type the heart rate is as a rule slowed at first in the transition from sinus rhythm to auriculoventricular dissociation. There are the usual blocked auricular beats that precede total dissociation, and later, when the ventricles beat independently of the auricles, there is a further slowing of the heart rate. Finally, before ventricular fibrillation appears, acceleration ensues as a result of the interposition of multiple premature beats.

The alterations in rhythm that precede transient periods of ventricular fibrillation during established auriculoventricular dissociation are brought about by (a) an increase in the basic idioventricular rate, (b) the interposition of premature beats which at first come singly and then in groups and, finally, (c) by ventricular oscillations which, in the final analysis, appear to be short runs of ventricular fibrillation.

The idioventricular rate may at times be accelerated in the prefibrillatory period, and this acceleration may be brought about through a variety of mechanisms that have been described elsewhere.[7] Obviously, a study of the effects of any drug upon the cardiac mechanism in patients with established auriculoventricular dissociation must take into account the inherent variability of the idioventricular pacemaker in such patients at a time when they are free from the symptoms that follow ventricular fibrillation. It should be emphasized that our ob-

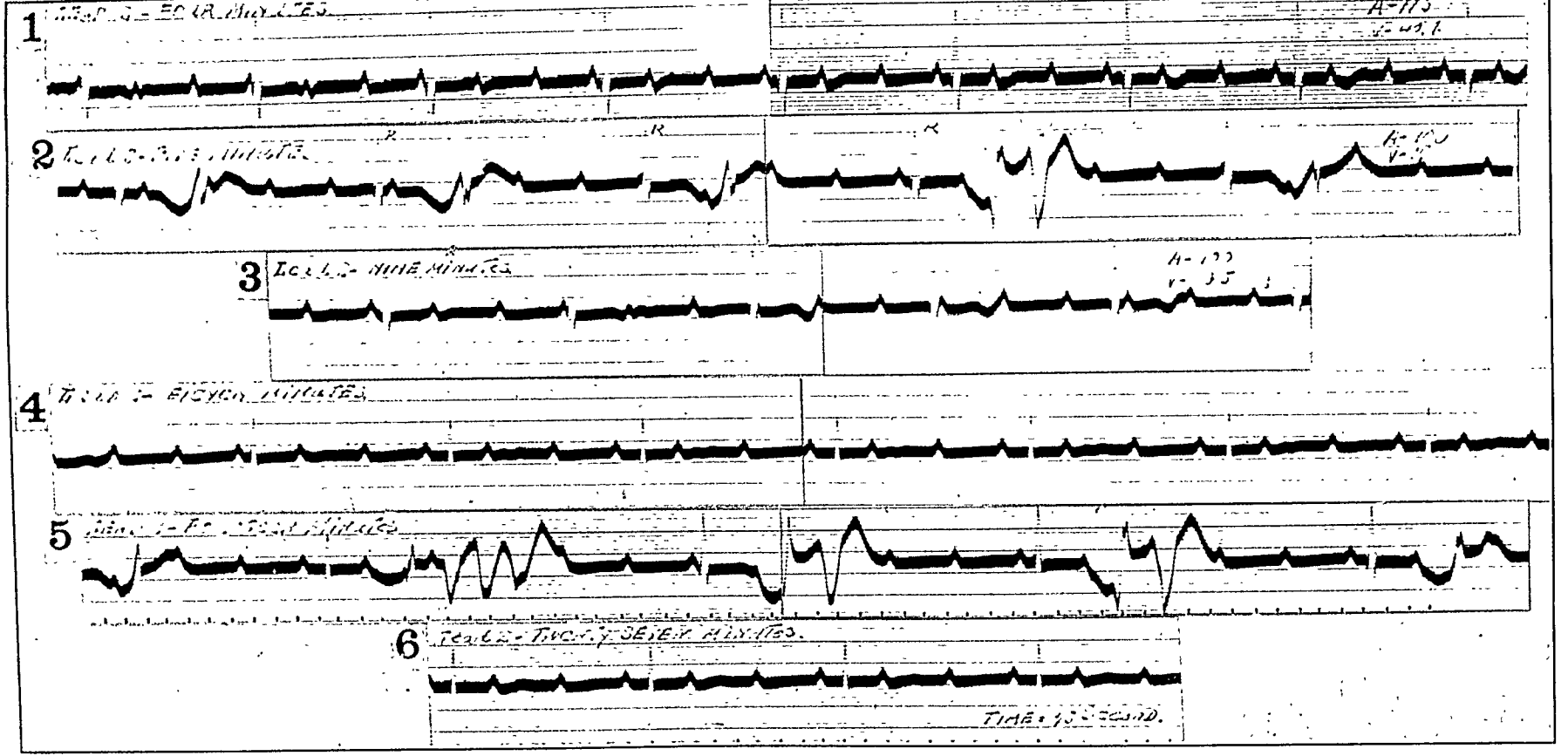

Fig. 1.—A series of electrocardiographic tracings (Lead II only) obtained after the intravenous administration of digifolin to a patient with normal sinus rhythm.

Strip 1: Four minutes after injection of 0.5 c.c. of digifolin. A regular sinus rhythm with a rate of 84 beats per minute is converted to heart block with a ventricular rate of 40.7 and an auricular rate of 115.

Strip 2: Five minutes after the injection of 0.5 c.c. of digifolin. The basic ventricular rate is now 16 beats per minute. The auricles have slowed to 100. Note the interposition of ventricular premature beats.

Strip 3: Nine minutes after the injection of 0.5 c.c. of digifolin. There is a transient return to a heart block with a ventricular rate of 35; the auricular rate is still 100.

Strip 4: The heart block persists for two minutes.

Strip 5: Short runs of ventricular fibrillation begin to disrupt the basic rhythm. Note the markedly aberrant ventricular complexes which follow the basic complexes.

servations were limited to patients in whom some form of dissociation of the auricles from the ventricles was invariably present before the type of fibrillation with which we are concerned set in.

THE EFFECTS OF DIGITALIS BODIES ON A PATIENT WITH NORMAL SINUS RHYTHM WHO DEVELOPED VENTRICULAR FIBRILLATION DURING TRANSIENT AURICULOVENTRICULAR DISSOCIATION

The intravenous administration of 0.5 c.c. of digifolin (the equivalent of ½ cat unit) or of 0.25 mg. (1/240 grain) of ouabain was sufficient to change a normal sinus rhythm to partial heart block in a patient who usually showed this transition prior to the development of transient ventricular fibrillation (Fig. 1, strip 1). The same phenomenon was observed in this patient when the experiment was repeated one year later. The injection of 1 c.c. of digifolin yielded the same results. Within four minutes following the administration of either drug there was a sudden change from sinus rhythm with a rate of 90 beats per minute to partial auriculoventricular dissociation with a ventricular rate of 40.7 and an A-V ratio of 3:1. The form of the basic ventricular complexes indicated that the impulse which gave rise to them was supraventricular in origin and that the main ventricular deflections were diphasic. The average R-T segment measured 0.36 sec. and the T-waves (when not masked by a superimposed auricular contraction) were only slightly negative.

One minute later the basic ventricular rate fell to 16 beats per minute (average) and the auricular rate slowed to 100. The ventricular complexes were now diminished in height; the R-T segment was considerably prolonged; and the T-waves assumed a pronounced negativity and were distorted by the superimposed auricular complexes, as well as by the bizarre single and coupled (Fig. 1, strip 2) premature beats of the ventricles that began to disrupt the auriculoventricular dissociation.

These bizarre complexes were in every respect similar to those observed in this patient prior to the spontaneous development of her transient ventricular fibrillation.

During the next six minutes the ventricular beating became regular, and the rate increased to an average of 35 per minute before another paroxysm of ventricular fibrillation occurred (Fig. 1, strips 3 and 4). Clinically, these aberrant ventricular oscillations were frustrate, and consequently they produced no audible sound at the apical region of the heart or perceptible pulse (Fig. 1, strip 5).

On another occasion, fourteen and a half minutes at one time, and twenty minutes at another, after the injection of these drugs, the recurrent ventricular oscillations increased in frequency and duration, so that the intersphygmic intervals became longer. As a result, the patient shut her eyes momentarily, and her face assumed a deathly pallor from the ineffectual distribution of blood to the periphery.

On two separate occasions, twenty-seven minutes and nineteen minutes, respectively, after the administration of the drugs, there were attacks of complete unconsciousness, associated with ventricular fibrillation, which lasted twenty-five and twelve seconds, respectively.

Throughout the rest of the day on which these experiments were carried out the cardiac mechanism was constantly being interrupted by short runs of ventricular fibrillation, a phenomenon that was observed to follow the use of other drugs in such patients.[8, 9] On two such occasions complete restoration of normal sinus rhythm required three or four days.

In this patient no attempt was made to introduce the drugs into the circulation when any abnormal rhythms were present, since at this stage of the patient's illness (she was in the hospital for four and a half years) she invariably developed severe congestive heart failure after having short runs of ventricular fibrillation.

THE EFFECTS OF DIGITALIS BODIES ON PATIENTS WITH ESTABLISHED AURICULOVENTRICULAR DISSOCIATION WHO SHOWED RECURRENT SEIZURES OF TRANSIENT VENTRICULAR FIBRILLATION

The response of patients with auriculoventricular dissociation to the intravenous administration of digifolin and ouabain in the doses described above was variable from time to time, and in the same patient the irregularities induced by the drugs appeared at variable intervals. The onset of the preliminary abnormal rhythms that led to ventricular fibrillation, such as premature beats of the ventricles and short runs of ventricular oscillations, invariably coincided with a slowing of the auricular rate, indicating that these disturbances were caused by the same factor, namely, the administration of digitalis bodies, and were not spontaneous. The time of the appearance of the abnormal rhythms after the injection of the drugs averaged from fourteen to twenty-one minutes. As in the previous patient, once these abnormalities began to appear, they facilitated the development of short runs of ventricular fibrillation which increased in duration and frequency as the day passed and were accompanied at times by periods of unconsciousness when the duration of the intersphygmic intervals exceeded 8 to 20 sec.

Repeated attempts were made to study the effects of the drugs at times when both spontaneous ventricular premature beats and auriculoventricular dissociation were present, but, unfortunately, no correlation could be established between the drug effect and the development of the abnormal mechanism. Since premature beats in themselves very likely facilitate the occurrence of ventricular fibrillation in such patients, with a variable time interval between their inception and that of the fibrillatory process, a correlation could not be established. Suffice it to say that digitalis bodies when injected intravenously did not abolish these abnormal mechanisms at any time.

DISCUSSION

These observations reveal that in patients who are subject to transient seizures of ventricular fibrillation *small* doses of either digifolin or ouabain, administered intravenously, are able to initiate the abnormal mechanism. That the dose need not be large is also indicated by previous observations that ventricular fibrillation may follow the intravenous use of digitalis preparations. For example, von Hoesslin[10] gave only 0.4 mg. of strophanthin K intravenously to a patient who ten minutes later complained of light pains in the precordial region. The electrocardiogram obtained at this time revealed normal rhythm with a ventricular rate of 142 beats per minute. Twenty-five minutes later ventricular fibrillation set in, and ten minutes after that the heart showed no signs of any electrical activity. Von Hoesslin emphasized the fact that the dose need not be large and that fibrillation of the ventricles may begin as late as twenty to thirty minutes after the injection. Similarly, Penati[11] recorded a ventricular tachycardia of 165 to 170 beats per minute in a 42-year-old woman with auricular fibrillation and ventricular extrasystoles who received only 1.8 mg. of strophanthin intravenously. The sudden death of this patient was in all probability due to ventricular fibrillation, for electrocardiograms obtained while she was dying revealed this mechanism. However, attention should be called here to the fact that the tachycardia which is a manifestation of digitalis intoxication need not end in ventricular fibrillation, as is commonly believed.[12] Experiences at the Montefiore Hospital lead us to conclude that in such cases the cause of death is as likely to be ventricular standstill as ventricular fibrillation.[13]

It is very obvious from a study of the natural course of patients who are subject to transient seizures of ventricular fibrillation that some form of block is an essential factor in the attacks. Yet in patients with "block" whose advanced ventricular arrhythmias do not lead to such attacks, the amounts of digitalis used in our experiments never produced ventricular fibrillation. Indeed, it would appear from previous studies of the effect of digitalis on patients with complete heart block that the drug must be used in more than the ordinary therapeutic dose in order to precipitate such abnormal mechanisms.[14] It is evident that the factors responsible for ventricular irregularities in patients with transient seizures of ventricular fibrillation after the injection of small doses of digitalis are as yet not understood.

SUMMARY AND CONCLUSIONS

1. Digifolin and ouabain were administered intravenously to three patients who were subject to transient seizures of ventricular fibrillation, at a time when the basic cardiac mechanism was relatively fixed.

2. Small doses of digifolin (0.5 c.c., the equivalent of ½ cat unit) and ouabain (0.25 mg.), when given intravenously to a patient who

usually showed normal sinus rhythm when she was free from attacks, caused partial heart block within four minutes. After the block became complete, short runs of ventricular fibrillation appeared in this patient within fourteen to twenty-five minutes after the injection.

3. The same doses, when administered to two patients with established auriculoventricular dissociation, caused short runs of ventricular fibrillation within fourteen and a half to twenty-seven minutes after injection.

4. The time of the appearance of the advanced ventricular irregularities was very variable, but the average was eighteen minutes.

5. The administration of these drugs at a time when these patients were having isolated premature beats during established auriculoventricular dissociation did not abolish the abnormal mechanism.

6. Since the intravenous injection of digitalis bodies favors the development of transient ventricular fibrillation in patients who are subject to it, the use of the drug is contraindicated in such patients.

7. The factors responsible for the development of ventricular fibrillation in such patients following the administration of digitalis and ouabain are still unknown.

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FACTORS OF ERROR IN BLOOD PRESSURE READINGS*†

A Survey of Methods of Teaching and Interpretation

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THE purpose in the presentation of this problem is to emphasize the need for a universal standardization of the methods used in the measurement of blood pressure. We have made an effort to determine what variations ordinarily occur in the making of blood pressure observations by interns, attending physicians, and postgraduate medical students in a large postgraduate institution; second, to ascertain how this procedure is taught by medical schools; and third, how it is prescribed by other (medical) institutions which are vitally interested in this subject, such as the life insurance companies. No attempt is made to recommend a standardized method of procedure.

Throughout the country, the most widely accepted and practiced method of measuring blood pressure is the auscultatory method described by Korotkoff in 1905, with the use of a rubber cuff, attached either to a mercury or aneroid manometer, and a stethoscope. In a critical study of blood pressure readings as recorded in various hospital charts by different attending and house physicians, many discrepancies were found. In fact, there was greater variation than the regular limits of error would allow. This latter finding provided the stimulus for this investigation.

It was decided to test the methods employed in taking blood pressure readings by various members of a large general hospital. The New York Post-Graduate Hospital was considered suitable because it is abundantly supplied with physicians from all parts of the world and from many different medical schools. It was decided to make the experiment among three groups: (1) interns, (2) postgraduate students, and (3) attending physicians.

TECHNIQUE

Experiment I. To obviate some of the sources of error a multiaural stethoscope was used so that four different observers could listen to the sounds at the same time on the same patient. The diaphragm of the stethoscope was always placed over the previously palpated brachial

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artery. Effort and attention were concentrated mainly upon the interpretation of the systolic and diastolic phases.

Experiment II. In this experiment an effort was made to record the readings of a large number of observers making blood pressure measurements simultaneously on the same patient. The Cambridge amplifying stethoscope was used. The dial of a Tycos desk manometer was projected on a screen. The cuff was then placed on the arm of the patient and inflated. The stethoscope was placed over the previously palpated brachial artery.

Cards were filled out by the observers, stating from what medical school they graduated, the year of their graduation and their present affiliations, the results of their findings, and how they derived the systolic

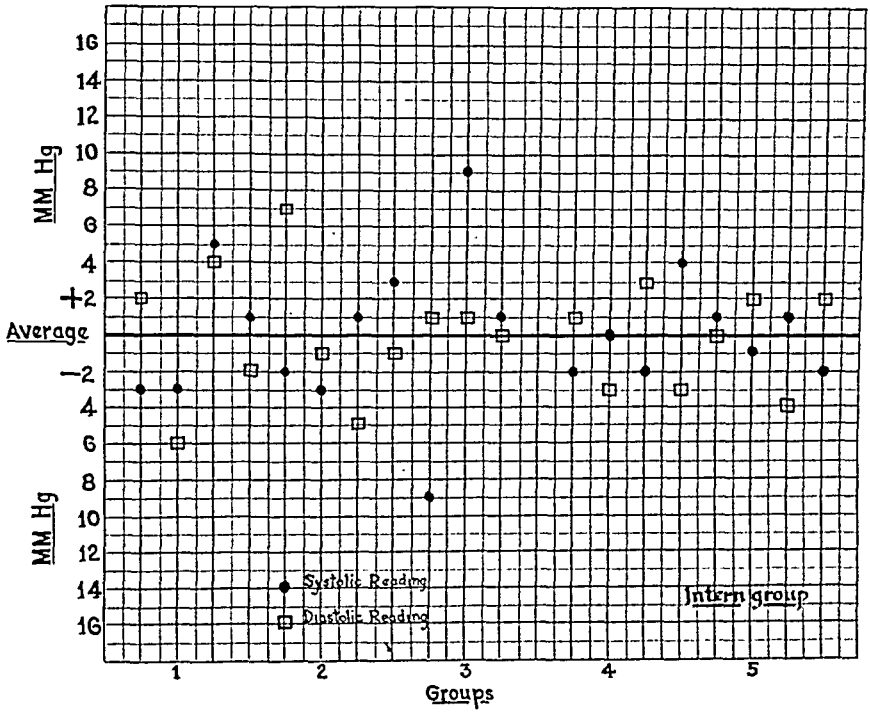

Chart 1.—Experiment 1A. Showing variation in recorded results when four interns at a time took blood pressure readings according to their individual methods of interpretation.

In all charts the average of each set of readings is represented as the "Average" line. The deviations in mm. of Hg for both systolic and diastolic are plotted from this.

and diatolic readings. They were also asked not to make any comparison or communication concerning their results before recording them.

Charts 1 to 5 indicate in graphic form the deviation from the average in millimeters of mercury.

The patients were not selected for this study. They were chosen at random, but patients suffering with hypertension and auricular fibrillation, as well as patients with apparently normal circulatory systems, were included. In single experiments differences in diastolic readings amounting to as much as 20 mm. of mercury, and in systolic readings to as much as 16 mm. of mercury, were observed.

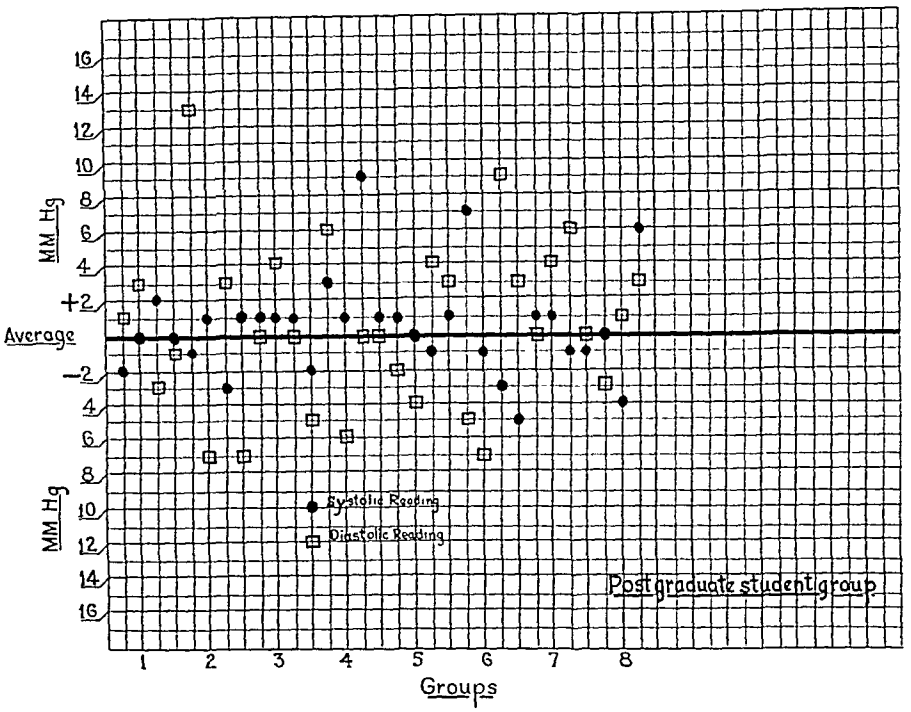

Chart 2.—Experiment 1B. Same as 1A, observations by postgraduate medical students from widely scattered areas.

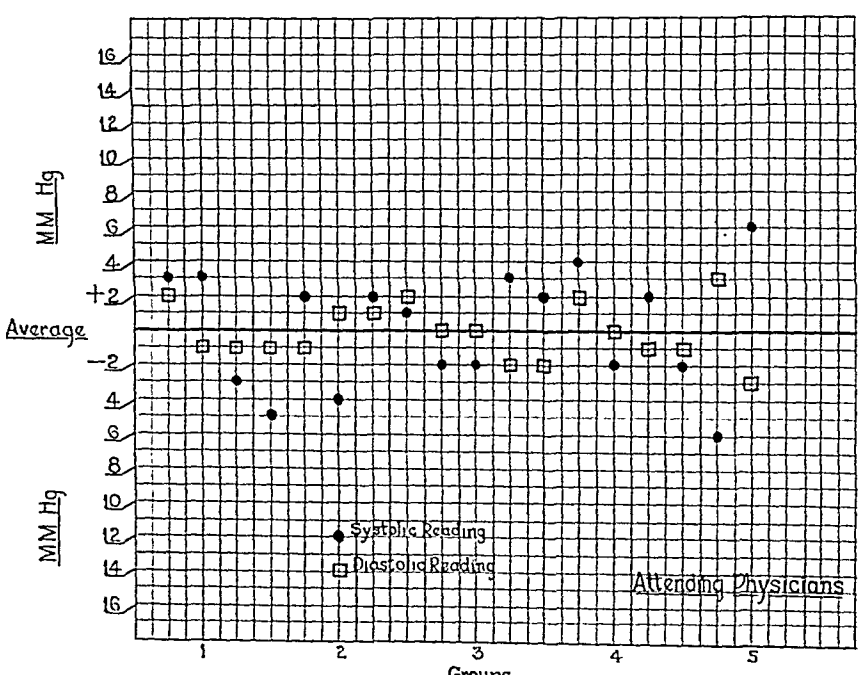

Chart 3.—Experiment 1C. Same as 1A, observations by attending physicians on the Medical Service of the New York Post-Graduate Hospital.

In correlating the methods of determination of the diastolic and systolic phases, which merely meant the interpretation of the sounds as they came through beneath the cuff, the following criteria were used:

Intern Group		
Systolic:	1st sound heard	90%
	1st loud sound heard	10%
Diastolic:	Sudden muffling of sound (4th phase)	90%
	Disappearance of sound (5th phase)	10%
Attending Physician Group:		
Systolic:	1st sound heard	90%
	1st loud sound heard	10%
Diastolic:	Sudden muffling of sound (4th phase)	50%
	Disappearance of sound (5th phase)	50%
Postgraduate Group		
Systolic:	1st sound heard	75%
	1st loud sound heard	25%
Diastolic:	Sudden muffling of sound (4th phase)	52%
	Disappearance of sound (5th phase)	48%

This study not only showed a marked difference in criteria, but also a wide variation in the interpretation of the sounds. Consequently, the next step to be taken was obvious. With the consent and encouragement of the Executive Committee of the American Heart Association, questionnaires were sent to the directors of the medical departments of forty of the leading medical schools of this continent, in an attempt to find out whether there exists a standard method of measuring blood pressures for all the schools and within each school. To date, twenty-four answers have been received.

If the results obtained by the use of the four-way stethoscope were surprising, the replies from the medical schools were even more so, and in a way explained the variations which we had observed.

Of the twenty-four replies, in 67 per cent it was stated that a standard method was employed and taught in the medical department, and in 33 per cent that no standard method was taught. It should be pointed out that the schools with standard methods varied widely in their opinions as to which methods should be used. Eighty-three and one-third per cent of those replying agreed that the first sound heard marked the systolic pressure. Sixteen and two-thirds per cent taught differently in cases of disordered rhythm and hypertension. The diastolic level was taken in 62.5 per cent as the point where the sounds suddenly become muffled (4th phase). Twelve and one-half per cent taught that the disappearance of the sound (5th phase) marked the diastolic pressure, and 25 per cent

taught that either the 4th or 5th phase could be interpreted as indicating the diastolic level, which would be very confusing. One school taught that the loudest sound was the diastolic point, and another school stated merely that the interpretation of the diastolic pressure was "variable."

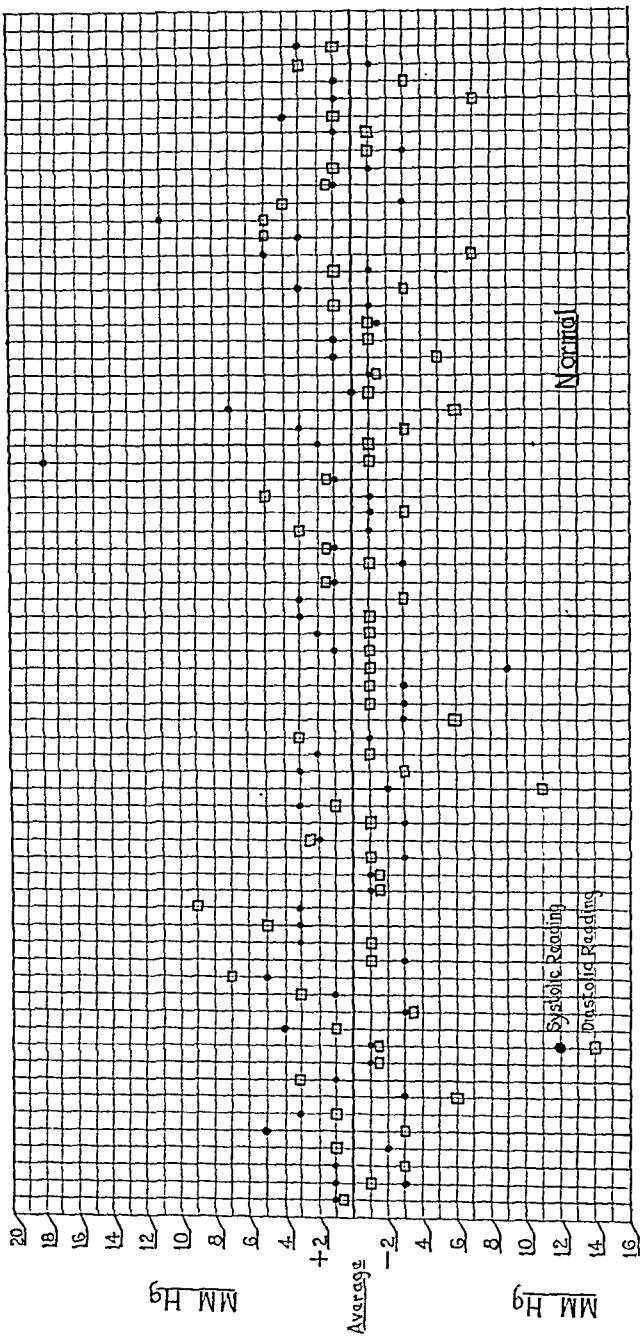

Chart. 4.—Experiment 2A. Simultaneous observations made by 68 physicians on a normal subject by means of a loud-speaker.

Further investigation has established the fact that some schools which claim to teach a standard method in practice actually do not. To quote a professor of a leading medical school: "At the same time I will make this prophecy, that the replies which you will get from those responsible for the clinical teaching in the universities will be a poor index of what

is actually taught. The replies will indicate that certain techniques are taught, but in actual practice each clinician follows his own preconceptions as to what is proper.''

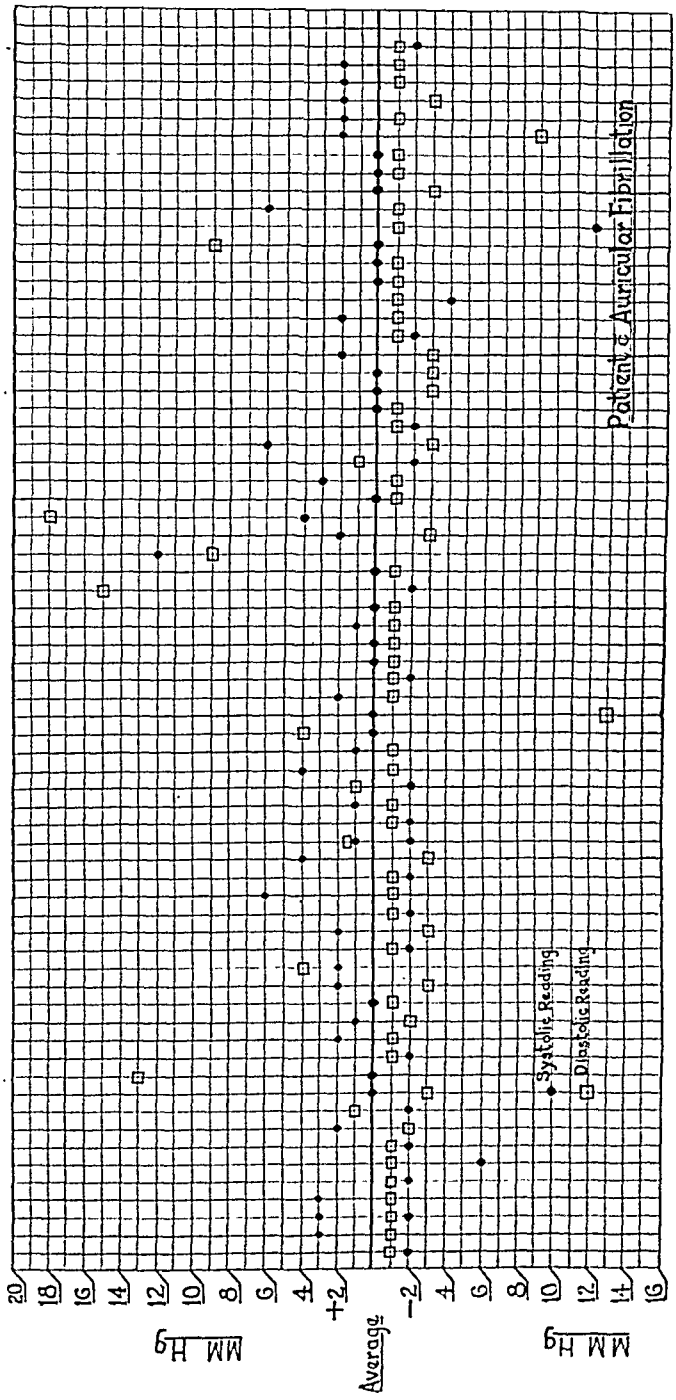

Chart 5.—Experiment 2B. Same as 2A. Patient with auricular fibrillation.

Other factors of error have been investigated by many clinicians. Erlanger,[1] in 1904, experimented with cuffs of different widths, varying from 5 to 17 cm. He found the error progressively less with increasing width of the cuff, but it did not seem to be entirely eliminated even with the 17 cm. cuff. In routine use a 12 cm. cuff was found to present the

smallest degree of error and was accepted as standard, since any cuff of greater width was found to be impractical. Hensen,[2] Janeway,[3] and Hill and Flack[4] showed that, in the absence of edema and muscular contraction and with a sufficiently wide cuff, the size of the arm makes little difference in the reading. Kilgore,[5] in 1918, pointed out the relative merits of the palpatory and auscultatory methods for determining the systolic pressure. Erlanger[1] showed that systolic readings taken while slowly inflating the cuff are usually a little higher than those obtained with falling pressure. Time does not permit a review of the volumes of literature written on the sources of error in blood pressure determinations. Despite these volumes, however, there is no agreement in medical schools today as to what methods should be taught or used clinically or in research.

This problem is, of course, of vital interest and importance to the life insurance companies. A discrepancy of 16 mm. of mercury in the systolic readings and 20 mm. in the diastolic readings, which occurred in one of our experiments, would place an applicant in one of three categories: (1) So-called standard group, with the payment of the ordinary premium; (2) substandard, with an increased premium; or (3) outright declination. Mortality statistics compiled by actuaries have shown that when the systolic pressure is 10 mm. Hg above the average the attained mortality exceeds the expected mortality, and that the percentage of this increase in the attained mortality rises with every increase of 5 mm. in the systolic pressure. This is also true of the diastolic pressure and when both exceed the average the mortality is even greater.

A questionnaire modified from the one used for medical schools was sent to the medical directors of one hundred insurance companies; eighty-two responded, and the replies show that the insurance companies are instructing their examiners differently, as follows:

Of the eighty-two medical directors who replied, thirty-seven, or 45 per cent, stated that they employed a standard method, whereas forty-five, or 55 per cent, declared that their examiners used various criteria. Again the standard methods used varied widely. The systolic pressure was designated by forty-nine companies as the level at which the first sound is heard during deflation of the cuff, by six as that at which the last sound is heard during inflation of the cuff, and by two as that at which the sounds are loudest during deflation. Twenty-five companies confessed that they had no idea how their examiners measured systolic pressure.

The diastolic pressure was designated by forty-eight companies as the point at which the sounds disappear (5th phase), and by six as the 4th phase in cases in which the sounds become muffled suddenly. Sixteen companies required their examiners to report the pressure at both the 4th and 5th phases, and twelve did not know how their examiners were measuring diastolic pressure. The confusion here is no worse than that which exists in the medical schools. Many companies took occasion to

emphasize the fact that the blood pressure is variable when the pulse is irregular; several insisted that the auscultatory method be checked by palpation. Several respondents in the latter group, however, indicated that the blood pressure observations should be made as the arm is being compressed, rather than decompressed.

An interesting commentary was made by three of the companies that their older examiners made the most errors in measuring blood pressure.

That there are marked discrepancies in the making and interpreting of blood pressure observations is beyond dispute. This fact has been known for a long time. Cook,[6] reporting to the Life Insurance Medical Directors Association in 1921, stated that not only were the insurance companies instructing their examiners differently, but that teachers of medicine were not in agreement as to the best methods of measuring blood pressure. He recommended that the Medical Directors Association address a communication to the Association of American Medical Colleges reciting the confusion arising from this failure to standardize such an important clinical procedure and requesting their comments on the subject. We can find no evidence to show that the Medical Colleges took any action at that or any other time.

Clearly, then, this is a problem for the teaching institutions. Individuals cannot be standardized, but procedures for observing their biological processes can be, within certain limits. Important basic biologic measurements should be uniform whenever possible, and they should be so taught in the medical colleges and universities. The making of blood pressure readings is one of the most common procedures in medical practice and research. In the United States and Canada essentially the same equipment is utilized by practically all physicians. The great differences in results as above demonstrated arise for the most part from the confusion as to what is the proper method of measuring blood pressure. The solution is simple providing certain steps are taken. We respectfully submit that the proper officers of the American Heart Association consider the appointment of a National Committee to study this problem for the purpose of taking the steps necessary to provide a standard method of measuring blood pressure for the use of teachers and practitioners of medicine.

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THE EFFECT OF VALVULAR HEART DISEASE ON THE DYNAMICS OF THE CIRCULATION

Observations Before, During and After the Occurrence of Heart Failure*

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IT IS common experience that organic valve defects frequently lead to heart failure, and it has been found that, when this has occurred, the volume output of blood from the heart is decreased.[1, 2] The effects of the valve lesions on the circulation before the onset of failure, however, have not been sufficiently studied. This was apparent when Grollman[3] reviewed the data available in 1932. Starr and his coworkers[4] have made measurements of output in 7 patients with valvular defects before the onset of failure, and Stewart and his associates[5] have also made a few such measurements, but there has been no study of a large series of cases. We have, therefore, made certain measurements of the circulation in 40 patients exhibiting the organic valvular lesions commonly encountered. None had experienced congestive heart failure or was taking drugs. Normal sinus rhythm was present in all. In one (H. W.) the etiology was syphilis, in a second (J. F.) the defect was congenital (coarctation of the aorta), and in the remaining 38 the lesions were those associated with rheumatic infection (Table I). In our analysis, stenosis of a valve is recorded as a lesion and insufficiency as another, so that when both stenosis and insufficiency were present, the patient was said to have two lesions. Five of the patients had single valve lesions, 2 had aortic stenosis and aortic insufficiency, and one had coarctation of the aorta; of the remaining 32, 11 suffered from mitral stenosis and mitral insufficiency, 9 from mitral stenosis and mitral insufficiency and aortic insufficiency, and 12 from mitral stenosis and mitral insufficiency and aortic stenosis and aortic insufficiency (Table I).‡ Only those cases were studied in which the diagnosis of the valve lesion was unequivocal.

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‡In the text of the paper M. I. = mitral insufficiency; M. S. = mitral stenosis; A. I. = aortic insufficiency; A. S. = aortic stenosis; M. S., M. I. = mitral stenosis and mitral insufficiency, etc.

In order to detect differences in functional capacities in progressive heart disease, we have also compared the mitral stenosis and insufficiency group before the onset of failure with a group having the same valve defect after recovery from failure, and with another during congestive heart failure.

We have accumulated the following data under basal conditions: cardiac output, basal metabolic rate, heart rate, height and weight, circulation time, venous pressure, cardiac size in teleoroentgenograms, arterial pressure, physical signs and electrocardiogram.

Thirteen normal individuals were used as controls. A complete report of the observations made in this group will be published elsewhere.[6]

METHODS

All observations were made in the morning while the patients were in a basal metabolic state. All were admitted to the hospital for study. Measurements of the cardiac output* were made by the acetylene method, three samples of gas being

TABLE I

DISTRIBUTION OF CASES

Coarctation of aorta (congenital defect)		1	
Aortic insufficiency (1 rheumatic, 1 syphilitic)		2	
Aortic stenosis	Rheumatic or probably rheumatic	1	
Aortic stenosis and insufficiency		2	
Mitral insufficiency		1	
Mitral stenosis		1	
			8
Mitral stenosis and insufficiency		11	
Mitral stenosis and insufficiency and aortic insufficiency		9	
Mitral stenosis and insufficiency and aortic stenosis and insufficiency		12	
			32
Total			40
Normal individuals			13

taken as recommended by Grollman[3] and by Grollman, Friedman, Clark, and Harrison.[7] During the measurement the patients sat in a steamer chair (angle 135 degrees). They had been made familiar with, and trained to carry out, the procedures beforehand. While they were resting quietly, the cardiac rate was counted at intervals of five minutes. At the end of one-half hour the acetylene-air-oxygen mixture was rebreathed. Three samples of gas were taken during each rebreathing period for estimation of the arteriovenous oxygen difference. The first sample was taken after rebreathing ten to twelve times in 20 seconds, the second after two or three breaths more, and the third after two or three additional breaths. All three samples were usually obtained within 30 seconds. Samples were taken during expiration. The rebreathing procedure was carried out two or three times on each patient. Shortly afterward, the oxygen consumption was measured with a Benedict-Roth

*It is obvious that with this method of measuring the output of the heart in the presence of valve lesions the amount of "regurgitant" blood, which is not circulated through the lungs, cannot be estimated.

spirometer. After a short pause, the vital capacity was measured and height and weight recorded. In succession, sufficient time being allowed in the intervals for the patient to return to a basal metabolic state, an electrocardiogram was taken, the arm-to-tongue circulation time recorded, the venous pressure estimated, and the arterial pressure measured; finally, a roentgenogram of the heart was made at a distance of 2 m.

The arm-to-tongue circulation time was estimated by the use of decholin;[8] 5 c.c. of a 20 per cent solution were injected rapidly (1 to 2 seconds) through an 18 gauge needle into an antecubital vein while the patient was lying quietly in the supine position. This was repeated in one and one-half minutes after the response to the first test had been elicited. The time was recorded from the beginning of the injection until the patient perceived the bitter taste, since a minimal amount of the drug may give a response.

The venous pressure was measured by the direct method,[9] using a large antecubital vein, with the arm at the level of the right auricle. Normal pressures by this method range from 4 to 10 cm. of saline. The antecubital vein of one arm was reserved for the injection of decholin and of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the heart were taken with the patient in the standing position, during full inspiration, at a distance of 2 m.* Measurements of heart area were carried out by the technique of Levy[10] and estimations of volume were made as recommended by Bardeen.[11]

OBSERVATIONS RELATING TO VALVE DEFECTS BEFORE THE OCCURRENCE OF HEART FAILURE

The data are recorded in Tables II and III, and have also been plotted as frequency diagrams (Fig. 1).

The arteriovenous oxygen difference in the normal individuals averaged 61.4 c.c. (Tables II and III, Fig. 1). It increased to 68.2 c.c. in M. S., M. I., A. I., to 71.2 c.c. in M. S., M. I., and to 78.0 c.c. in M. S., M. I., A. S., A. I. In the few observations relating to the single lesions (to A. S., to A. I., and to M. S.), the arteriovenous oxygen difference did not change significantly; but, on the other hand, A. S., or A. I., or A. S., A. I., when combined with M. S., M. I., increased it.

The average cardiac index was 1.96 liters in M. S., M. I., A. I., 1.86 liters in M. S., M. I., and 1.72 liters in M. S., M. I., A. S., A. I. (Tables II and III, Fig. 1). The normal value is 2.11 liters.

The average stroke volume for the controls was 57 c.c. (Tables II and III, Fig. 1). It decreased to 47 c.c. in M. S., M. I., A. I., to 44 c.c. in M. S., M. I., and still further to 36 c.c. in M. S., M. I., A. S., A. I.

The average stroke volume per kilogram was 0.82 c.c. for normal individuals, but decreased to 0.75 c.c. in M. S., M. I., A. I., to 0.70 c.c. in M. S., M. I., and further still to 0.64 c.c. in M. S., M. I., A. S., A. I. (Tables II and III, Fig. 1).

*The authors are deeply indebted to the X-Ray Department of the New York Hospital for their cooperation in this investigation.

Table II

Data Relating to 40 Patients Exhibiting Valve Defects Before the Occurrence of Heart Failure

NAME, SEX, HISTORY NO., AGE	DATE	HEIGHT (CM.)	WEIGHT (KG.)	BODY SURFACE (SQ.M.)	OXYGEN CONSUMPTION (C.C. PER MIN.)	BASAL METABOLIC RATE (PER CENT)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC OUTPUT (LITERS PER SQ.-M. PER MIN.)	HEART RATE (PER MIN.)	STROKE VOLUME (C.C.)	CARDIAC AREA (SQ. CM.)	CARDIAC VOLUME (C.C.)	ARTERIAL PRESSURE (MM. HG)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM.)	VITAL CAPACITY (C.C.)	LEFT VENTRICULAR WORK (GM. M. PER BEAT)	STROKE VOLUME PER KG. (C.C.)	LEFT VENTRICULAR WORK PER BEAT PER KG. (GM. M.)	DIAGNOSIS*
Aortic Insufficiency																					
H. W. ♂	10/15/34	173.0	63.4	1.75	227	0	64.1	3.54	2.02	74	48	-	-	118/50	13.2	-	4100	55.0	0.76	0.87	Syph., A.I., E.H., Class I
No. 71726	10/16/34	172.5	63.1	1.75	232	+ 2	60.3	3.85	2.20	72	53	137.5	774.0	108/40	13.8	-	4100	53.0	0.86	0.84	
48 years	10/17/34	172.8	63.3	1.75	222	- 2	60.1	3.69	2.10	74	49	138.5	787.1	118/46	12.8	-	4250	55.0	0.77	0.87	
M. S. ♂	3/27/34	168.3	76.2	1.87	243	+ 5	53.6	4.53	2.43	84	54	176.8	1135.3	156/64	-	-	4290	80.8	0.71	1.06	Rh., A.I., marked E.H., Class IIA
No. 35859																					
27 years																					
Aortic Stenosis																					
V. T. ♂	12/ 4/37	168.3	61.2	1.78	255	+11	59.0	4.32	2.54	84	51	141.8	815.1	100/70	16.8	4.9	3500	59.0	0.83	0.96	Rh., A. S., E.H., Class IIA
No. 186110																					
33 years																					

*In this column the following abbreviations are used:

syph. = syphilis
Rh. = rheumatic fever
cong. = congenital
unk. = unknown
M.S. = mitral stenosis
M.I. = mitral insufficiency
A.S. = aortic stenosis
A.I. = aortic insufficiency
E.H. = enlargement of heart
sl. = slight
mark. = marked
? = questionable
R.I.V.H.B. = right intraventricular heart block
I, IIA, IIB, III, refer to functional classification (Criteria for the Classification and Diagnosis of Heart Disease, ed. 2, New York Tuberculosis and Health Association, New York, 1929).

TABLE II—CONT'D

Coarctation of Aorta																				
J. F. ♂ No. 63890 26 years	3/30/35	179.0	66.5	1.82	315	+24	90.3	3.52	1.93	89	41	274.6	2197.0	Rt. 174/60 Lt. 204/60	16.4	8.7	3250	69.7	0.62	1.04	Congenital, Coarctation of aorta, marked E.H., Class I
Aortic Stenosis and Insufficiency																				
W. M. ♂ No. 126827 47 years	3/30/36	165.0	53.5	1.59	245	+18	86.3	2.84	1.79	74	38	154.5	926.4	124/82	16.2	7.9	3500	53.2	0.71	0.99	Rh., A.S., & A.I., sl. E.H., Class I or IIA
J. M. ♂ No. 180633 32 years	10/ 5/37	162.5	78.0	1.84	309	+23	63.7	4.86	2.64	80	61	210.2	1470.3	118/50	15.6	8.2	3000		0.78	0.89	Rh., A.S., & A.I., E.H., Class I
Mitral Insufficiency																				
B. C. ♀ No. 84880 55 years	1/11/35	165.0	57.9	1.64	187	0	70.1	2.67	1.63	72	38	127.6	696.0	122/88	16.3	6.0	3400	54.3	0.66	0.94	Rh., M.I., Class I
Mitral Stenosis																				
R. D. ♂ No. 48714 32 years	12/11/33	184.0	61.8	1.82	237	- 5	61.4	3.86	2.12	66	59	121.2	647.0	105/60	-	-	4700	65.6	0.95	1.06	Unk., M.S., Class I
	10/30/36	182.3	60.4	1.80	234	- 5	61.8	3.79	2.10	70	54	129.6	714.4	102/70	12.7	6.9	4600 69.7	63.2	0.89	1.05	
Mitral Stenosis and Insufficiency																				
A. G. ♂ No. 79037 23 years	10/30/34	175.5	59.4	1.73	210	-14	69.9	3.00	1.74	76	39	144.0	832.1	118/80	16.0	-	4200	53.0	0.66	0.89	Rh., M.S., & M.I., E.H., Class I
	11/12/34	176.5	59.4	1.75	214	-10	69.7	3.06	1.79	76	40	141.9	811.0	118/74	18.5	-	4300	52.0	0.67	0.88	
	1/10/35	177.2	59.6	1.74	243	- 2	71.9	3.38	1.94	74	46	137.7	781.0	104/70	16.5	11.0	4200	46.7	0.77	0.78	
	3/28/35	176.0	61.7	1.74	222	-10	61.4	3.62	2.10	74	50	136.8	772.2	110/70	15.4	10.3	4200	61.2	0.81	0.99	
W. H. ♂ No. 37716 21 years	2/21/34	173.5	88.9	2.03	240	-13	71.7	3.34	1.65	88	38	114.8	595.0	122/90	-	-	4050	54.7	0.43	0.62	Rh., M.S. & M.I., Class I
M. H. ♀ No. 59670 39 years	3/28/34	155.0	50.7	1.48	170	- 8	63.7	2.67	1.81	80	33	130.9	724.0	108/70	-	-	2690	40.3	0.66	0.79	Rh., M.S. & M.I., sl. E.H., Class IIA

TABLE II—CONT'D

NAME, SEX, HISTORY NO., AGE	DATE	HEIGHT (CM.)	WEIGHT (KG.)	BODY SURFACE (SQ.M.)	OXYGEN CONSUMPTION (C.C. PER MIN.)	BASAL METABOLIC RATE (PER CENT)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC OUTPUT (LITERS PER SQ. M. PER MIN.)	HEART RATE (PER MIN.)	STROKE VOLUME (C.C.)	CARDIAC AREA (SQ. CM.)	CARDIAC VOLUME (C.C.)	ARTERIAL PRESSURE (MM. HG)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM.)	VITAL CAPACITY (C.C.)	LEFT VENTRICULAR WORK (GM. M. PER BEAT)	STROKE VOLUME PER KG. (C.C.)	LEFT VENTRICULAR WORK PER BEAT PER KG. (GM. M.)	DIAGNOSIS*
J. M. ♂ No. 79052 23 years	11/ 3/34	166.0	60.5	1.66	229	- 2	81.9	2.97	1.68	72	39	128.2	701.0	110/60	13.2	-	3700	45.1	0.64	0.75	Rh., M.S. & M.I. sl. E.H., Class IIA
W. L. ♂ No. 67123 20 years	9/29/34	171.5	60.3	1.72	220	-11	76.4	2.88	1.67	74	39	108.6	583.0	110/80	-	-	3400	50.4	0.65	0.84	Rh., M.S. & M.I. Class IIA
J. M. ♂ No. 85646 18 years	1/28/35	164.0	52.1	1.56	218	- 7	83.3	2.62	1.68	96	27	111.2	647.0	110/68	11.0	7.5	3500	32.7	0.52	0.63	Unk., M.S. & M.I. Class I
A. M. ♂ No.75530 24 years	9/28/35	178.0	71.0	1.88	203	-21	57.6	3.52	1.90	66	54	137.7	781.2	124/70	13.4	12.3	5000	71.2	0.76	1.00	Unk., M.S. & M.I. ? E.H., Class IIA
F. M. ♂ No. 66492 32 years	11/ 1/34	176.5	66.7	1.80	259	+ 6	81.4	3.18	1.77	70	45	138.2	784.4	122/72	14.0	-	4900	59.4	0.67	0.89	Rh., M.S. & M.I. Class IIA
J. T. ♂ No. 68162 20 years	6/28/34	176.0	71.6	1.86	273	+ 8	82.4	3.32	1.80	74	45	114.7	594.1	115/70	-	-	4900	56.9	0.63	0.79	Unk., M.S. & M.I., ? sl. E.H., Class I

TABLE II—CONT'D

C. W. ♂ No. 121630 23 years	3/25/36	174.3	59.7	1.72	255	+ 6	65.2	3.91	2.27	68	57	122.4	655.0	132/78	14.4	8.6	4200	81.4	0.95	1.36	Rh., M.S. & M.I., ? sl. E.H., Class I
R. T. ♀ No. 124470 29 years	3/14/36	167.0	54.0	1.60	218	+ 7	61.1	3.57	2.23	66	54	111.9	553.3	110/58	9.6	8.0	3000	61.7	1.00	1.10	Rh., M.S. & M.I., ? sl. E.H., Class I or IIA
Mitral Stenosis and Insufficiency; Aortic Insufficiency																				
A. B. ♂ No. 56690 23 years	4/10/34	174.6	63.5	1.77	207	-14	74.9	2.88	1.63	90	32	123.6	667.0	136/88	-	-	4650	48.7	0.50	0.77	Unk., M.S. & M.I., A.I., Class I
H. C. ♂ No. 82461 40 years	6/15/35	179.0	79.5	1.97	249	- 5	52.4	4.73	2.40	60	79	127.1	691.0	108/68	12.8	8.2	4700	94.6	0.99	1.19	Rh., R.I.V.H.B., M.S. & M.I., A.I., marked E.H., Class IIA
A. D. ♂ No. 149574 17 years	11/14/36	167.5	55.3	1.62	218	-13	75.0	2.91	1.80	54	54	119.5	632.0	125/68	16.0	5.4	4000	71.2	0.98	1.29	Unk., M.S. & M.I., A.I., ? sl. E.H., Class I
P. H. ♂ No. 63300 22 years	5/22/34	162.8	55.5	1.59	227	+ 5	64.7	3.51	2.21	70	50	148.3	872.0	122/74	-	-	3400	66.6	0.90	1.20	Rh., M.S. & M.I., A.I., E.H., Class IIA
J. L. ♂ No. 59220 25 years	4/19/34	169.5	58.8	1.68	238	+ 4	77.8	3.06	1.82	100	31	135.7	764.3	100/62	-	-	3940	34.2	0.53	0.58	Unk., M.S. & M.I., A.I., Class I
R. L. ♂ No. 90113 21 years	4/ 6/35	172.5	63.1	1.75	234	- 7	70.9	3.30	1.89	74	45	120.6	647.0	120/64	17.2	10.5	4100	56.0	0.71	0.89	Rh., M.I., M.S., & A.I., E.H., Class I
A. M. ♀ No. 37709 23 years	2/14/35	163.2	67.5	1.73	203	- 8	62.7	3.24	1.87	74	44	97.6	670.0	112/56	11.6	10.1	2900	52.0	0.65	0.77	Rh., M.I., M.S., & A.I., E.H., Class I or IIA

TABLE II—CONT'D

NAME, SEX, HISTORY NO., AGE	DATE	HEIGHT (CM.)	WEIGHT (KG.)	BODY SURFACE (SQ.M.)	OXYGEN CONSUMPTION (C.C. PER MIN.)	BASAL METABOLIC RATE (PER CENT)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC OUTPUT (LITERS PER SQ. M. PER MIN.)	HEART RATE (PER MIN.)	STROKE VOLUME (C.C.)	CARDIAC AREA (SQ. CM.)	CARDIAC VOLUME (C.C.)	ARTERIAL PRESSURE (MM. HG)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM.)	VITAL CAPACITY (C.C.)	LEFT VENTRICULAR WORK (GM. M. PER BEAT)	STROKE VOLUME PER KG. (C.C.)	LEFT VENTRICULAR WORK PER BEAT PER KG. (GM. M.)	DIAGNOSIS*
F. R. ♂ No. 47031 26 years	1/26/34	166.0	66.7	1.75	219	- 8	77.5	2.83	1.62	72	40	141.1	809.0	130/64	-	-	4350	52.8	0.60	0.79	Rh., M.S. & M.I., A.I., E.H., Class I
H. W. ♂ No. 44299 29 years	1/ 4/35	174.0	60.4	1.72	238	0	57.9	4.18	2.43	80	52	149.1	779.0	128/60	13.0	8.3	3900	66.5	0.86	1.10	Rh., M.S. & M.I., A.I., sl. E. H., Class I
Mitral Stenosis and Insufficiency; Aortic Stenosis and Insufficiency																					
E. P. ♂ No. 14505 21 years	11/ 8/34	167.0	49.3	1.54	195	-12	71.4	2.73	1.77	80	34	119.2	629.0	122/50	19.5	-	3100	40.0	0.69	0.81	Rh., M.I., M.S., A.I., & A.S., E.H., Class IIA
M. C. ♀ No. 67280 46 years	12/10/34	156.5	47.0	1.44	182	+ 5	77.4	2.35	1.63	66	36	125.8	678.4	128/84	15.6	6.7	2600	52.0	0.77	1.10	Rh., M.I., M.S., A.I., & A.S., E.H., Class IIA
J. F. ♀ No. 31027 25 years	5/18/35	164.0	46.3	1.48	122	0	65 9	1.85	1.25	70	26	121.6	647.0	104/50	16.6	6.8	2800	27.0	0.56	0.58	Unk., M.I., M.S., A.I., & A.S., E.H., Class I

TABLE II—CONT'D

E. C. ♀ No. 33078 19 years	3/18/35	164.0	61.0	1.66	195	- 6	82.8	2.36	1.42	86	27	106.9	551.2	104/10	10.7	8.2	2850	21.0	0.44	0.34	Rh., M.I., M.S., A.I., & A.S., E.H., Class I
J. C. ♂ No. 124678 28 years	12/ 9/37	172.4	79.9	1.88	331	+21	75.5	4.15	2.21	80	52	113.0	580.4	128/30	16.4	7.6	4000	55.9	0.65	0.70	Rh., M.S. & M.I., A.S. & A.I., E.H., Class I
E. F. ♂ No. 67656 29 years	6/22/34	167.8	49.0	1.56	253	+18	84.7	2.99	1.90	94	32	247.6	1882.0	130/30	-	-	3100	34.8	0.65	0.71	Rh., M.S. & M.I., A.S., & A.I., marked E.H., Class IIA
I. G. ♂ No. 43913 43 years	6/27/34	163.0	61.2	1.68	249	+16	79.0	3.15	1.87	93	34	168.6	1055.0	155/35	-	-	3700	43.9	0.56	0.72	Rh., M.S. & M.I., A.S. & A.I., E.H., Class IIA
J. H. ♂ No. 28858 20 years	4/11/34 4/15/34 4/18/34	181.5 181.5 181.5	60 8 61.3 61.0	1.79 1.79 1.79	253 251 234	+ 3 + 3 - 4	80.8 90.0 81.9	3.12 2.80 2.86	1.75 1.56 1.60	80 83 84	39 34 34	180.0 180.0† 180.0†	1178.0 1178.0† 1178.0†	166/50 162/40 152/40	- - -	- - -	4300 4230 4210	57.3 46.7 44.4	0.64 0.55 0.56	0.94 0.76 0.73	Rh., M.S. & M.I., A.S. & A.I., E.H., Class IIA
S. H. ♂ No. 58578 45 years	1/ 3/35	179.5	54.2	1.70	218	- 1	81.5	2.67	1.57	84	32	151.5	899.4	86/72	25.0	10.2	2450	34.4	0.59	0.65	Unk., M.S. & M.I., A.S., & A.I., E.H., Class IIA
H. N. ♂ No. 52501 14 years	2/ 6/34	158.5	42.2	1.39	232	+ 5	86.4	2.68	1.93	94	29	124.1	668.0	138/32	-	-	2970	33.5	0.69	0.79	Rh., M.S. & M.I., A.S. & A.I., ? E.H., Class IIA
J. O. ♂ No. 124373 31 years	3/ 7/36	169.7	54.4	1.62	203	- 8	77.7	2.61	1.61	60	44	170.8	1070.1	96/70	22.9	7.3	2500	49.7	0.81	0.91	Rh., M.S. & M.I., A.S. & A.I., E.H., Class IIA
M. S. ♂ No. 30087 33 years	6/ 6/34	166.5	67.5	1.76	235	- 3	67.8	3.47	1.97	64	54	164.2	1015.0	108/60	-	-	3625	61.7	0.80	0.91	Rh., M.S. & M.I., A.S., & A.I., E.H., Class IIA

†X-rays not repeated on these days.

There was no significant deviation from the average normal venous pressure (10.0 cm.) in the patients with valve lesions (Tables II and III, Fig. 1).

The average arm-to-tongue circulation time in the normal subjects was 14.4 sec. There was a slight increase in patients with aortic stenosis, and in the M. S., M. I., A. S., A. I. group it was prolonged to 18.1 sec. (Tables II and III, Fig. 1).

In normal subjects the average work of the left ventricle per beat per kilogram was 1.04 gm.m. This was decreased to 0.95 gm.m. in M. S., M. I., A. I., to 0.88 gm.m in M. S., M. I., and further still to 0.78 gm.m in M. S., M. I., A. S., A. I. (Tables II and III, Fig. 1).

There was a tendency for the oxygen consumption to be greater in the patients with aortic lesions (Fig. 1).

TABLE III

MEAN VALUES OF MEASUREMENTS OF 13 NORMAL INDIVIDUALS* AND OF SUBJECTS EXHIBITING VALVE LESIONS BEFORE FAILURE (TABLE II)

	ARTERIO-VENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC INDEX (LITERS PER MIN.)	STROKE VOLUME (C.C.)	STROKE VOLUME (C.C. PER KG.)	LEFT VENTRICULAR WORK PER BEAT PER KGM. (GM.M.)	VENOUS PRESSURE (CM. PHYSIOLOGIC SALINE)	CIRCULATION TIME (SEC.)
Normal Individuals							
	61.4	2.11	57	0.82	1.04	10.0	14.4
Valve Lesions							
A.I.	59.5	2.19	51	0.78	0.91	-	13.3
A.S.	61.2	2.54	51	0.83	0.96	4.9	16.8
A.S. A.I.	75.0	2.22	50	0.75	0.94	8.0	15.9
M.I.	70.1	1.63	35	0.66	0.94	6.0	16.3
M.S.	61.6	2.11	56	0.92	1.06	6.9	12.7
M.S. M.I.	71.2	1.86	44	0.70	0.88	9.8	13.2
M.S. M.I. A.I.	68.2	1.96	47	0.75	0.95	8.5	14.1
M.S. M.I. A.S. A.I.	78.0	1.72	36	0.64	0.76	7.8	18.1

*Data from Stewart and Watson.[6]

OBSERVATIONS RELATING TO CHANGES ASSOCIATED WITH HEART FAILURE IN MITRAL STENOSIS AND MITRAL INSUFFICIENCY

Observations on groups of patients with mitral stenosis and insufficiency made before congestive failure had occurred, while it was present, and after recovery from failure, together with the same observations on the normal controls,[6] are summarized in Tables IV and V, and are also presented in the form of frequency diagrams (Fig. 2).

In the group of those who had recovered from heart failure, and in the group of those who had failure at the time of our study, there were patients with auricular fibrillation, as well as others with normal sinus mechanism. The rhythm is indicated in the frequency diagrams.

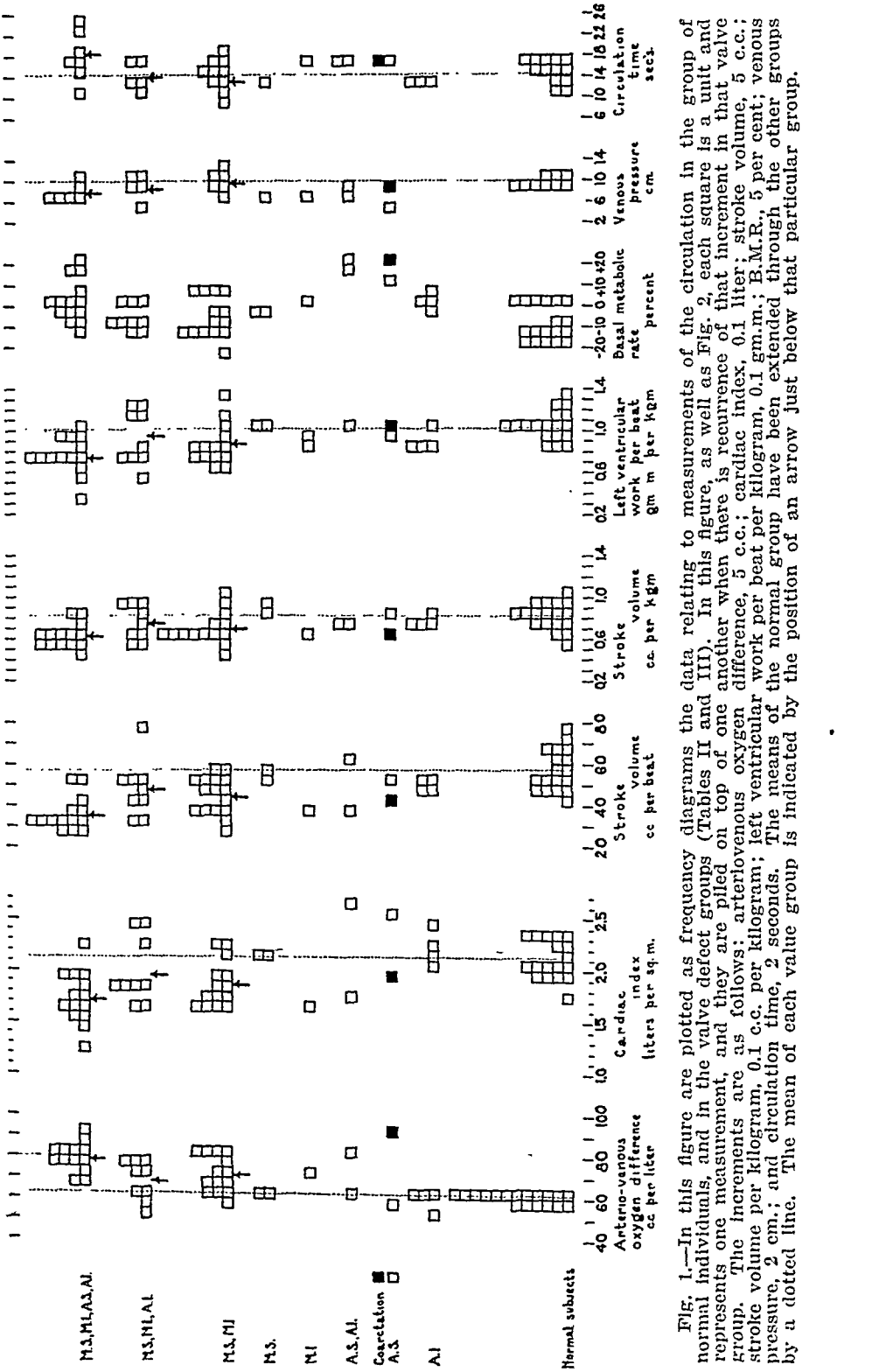

Fig. 1.—In this figure are plotted as frequency diagrams the data relating to measurements of the circulation in the group of normal individuals, and in the valve defect groups (Tables II and III). In this figure, as well as Fig. 2, each square is a unit and represents one measurement, and they are piled on top of one another when there is recurrence of that increment in that valve group. The increments are as follows: arteriovenous oxygen difference, 5 c.c.; cardiac index, 0.1 liter; stroke volume, 5 c.c.; stroke volume per kilogram, 0.1 c.c. per kilogram; left ventricular work per beat per kilogram, 0.1 gm.m.; B.M.R., 5 per cent; venous pressure, 2 cm.; and circulation time, 2 seconds. The means of the normal group have been extended through the other groups by a dotted line. The mean of each value group is indicated by the position of an arrow just below that particular group.

In Table V, averages of both normal sinus rhythm and auricular fibrillation are given, as well as the averages for the two rhythms combined. The combination of the two rhythms does not appear to alter the inferences from the analysis, but separation of the data is possible, if it is desired.

It is recalled that the average normal arteriovenous oxygen difference was 61.4 c.c. (Table V), and that it was increased to 71.2 c.c. in M. S., M. I. before failure. It was increased still further to 79.4 c.c. in those patients who had recovered from failure, and to 99.5 c.c. during heart failure (Tables IV and V, Fig. 2).

The average normal cardiac index amounted to 2.11 liters. In M. S., M. I., before failure, it was 1.86 liters; in those who had recovered from congestive heart failure it was 1.65 liters; and during congestive heart failure it was 1.39 liters (Tables IV and V, Fig. 2).

The average stroke volume amounted to 57 c.c. in normal individuals, but was decreased to 44 c.c. in M. S., M. I. before failure, to 43 c.c. in those who had recovered from congestive heart failure, and to 25 c.c. during failure (Tables IV and V, Fig. 2).

The average stroke volume per kilogram was decreased to 0.70 c.c. in M. S., M. I. before failure (normal, 0.82 c.c.), to 0.76 c.c. in those who had recovered from failure, and to 0.49 c.c. during failure (Tables IV and V, Fig. 2).

The left ventricular work per beat per kilogram was decreased to 0.88 gm.m in M. S., M. I. before failure (normal, 1.04 gm.m), to 0.91 gm.m. in those who had recovered from congestive heart failure, and to 0.68 gm.m. during congestive heart failure (Tables IV and V, Fig. 2).

The average venous pressure was increased to 12.8 cm. in congestive heart failure and was 7.3 cm. after recovery from failure (normal 10.0 cm.) (Tables IV and V, Fig. 2).

The circulation time showed no change from normal (14.4 sec.), in M. S., M. I. before failure (13.2 sec.), but was prolonged to 21.5 sec. in those who had recovered from congestive heart failure and to 27.5 sec. during failure (Tables IV and V, Fig. 2).

DISCUSSION

Analysis of the observations in the 32 cases falling in the M. S., M. I. and M. S., M. I., A. I. and the M. S., M. I., A. S., A. I. groups shows certain definite trends. With respect to arteriovenous oxygen difference, cardiac index, cardiac output per beat, stroke volume per kilogram and left ventricular work per beat per kilogram, the impairment was *least* in M. S., M. I., A. I., greater in M. S., M. I., and greater still in M. S., M. I., A. S., A. I. With respect to all these functions the

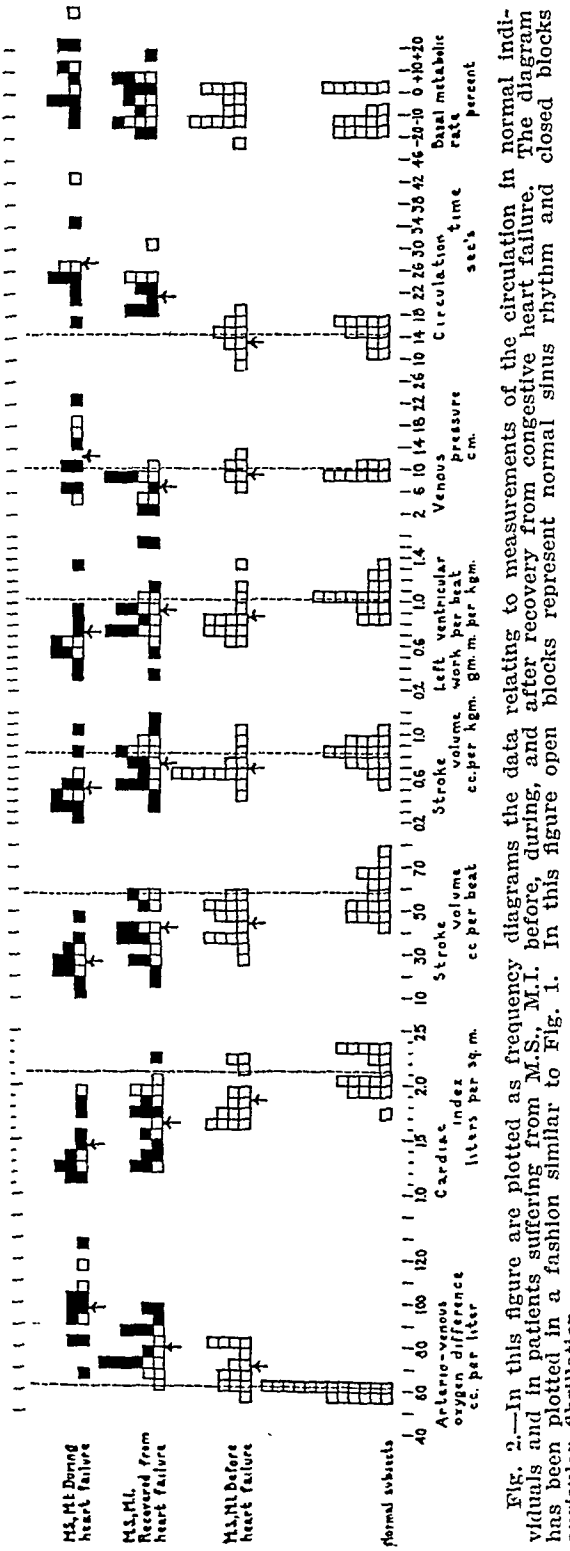

Fig. 2.—In this figure are plotted as frequency diagrams the data relating to measurements of the circulation in normal individuals and in patients suffering from M.S., M.I. before, during, and after recovery from congestive heart failure. The diagram has been plotted in a fashion similar to Fig. 1. In this figure open blocks represent normal sinus rhythm and closed blocks auricular fibrillation.

TABLE

DATA RELATING TO PATIENTS EXHIBITING MITRAL STENOSIS AND INSUFFI

NAME, HISTORY NUMBER, SEX, AGE	DATE	HEIGHT (CM.)	WEIGHT (KG.)	BODY SURFACE (SQ. M.)	OXYGEN CONSUMPTION (C.C. PER MIN.)	BASAL METABOLIC RATE (%)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC OUTPUT (LITERS PER SQ. M. PER MIN.)	HEART RATE (PER MIN.)	STROKE VOLUME (C.C.)	CARDIAC AREA (SQ. CM.)
												DURING CONGESTIVE
												Normal
S. S. No. 123829 ♂ 32 years	2/19/36	166.5	65.0	1.73	245	0	115.3	2.13	1.23	70	30	215.6
W. B. No. 131257 ♀ 32 years	4/28/36	151.0	53.8	1.48	207	+14	106.3	1.95	1.32	80	24	194.2
W. H. No. 64020 ♂ 24 years	9/23/35	166.0	44.9	1.47	263	+41	92.8	2.83	1.93	110	28	220.5
												Auricular
J. G. No. 16102 ♂ 28 years	3/13/35	163.0	54.3	1.57	272	+24	95.2	2.86	1.82	102	28	164.3
L. C. No. 36623 ♀ 30 years	3/ 4/35	165.2	60.3	1.66	222	+ 8	96.8	2.29	1.38	100	23	202.9
M. C. No. 119155 ♀ 53 years	1/28/36	147.7	67.3	1.61	207	+14	102.9	2.01	1.25	100	20	194.2
G. MacF. No. 124205 ♂ 57 years	2/25/36	163.0	49.9	1.52	189	- 2	84.2	2.24	1.47	64	27	158.6
J. M. No. 38715 ♂ 37 years	2/27/34	170.3	60.6	1.72	203	-14	100.5	2.02	1.17	76	27	218.0
M. P. No. 62815 ♀ 41 years	4/30/34	161.2	53.1	1.54	180	- 6	90.6	1.98	1.28	124	16	173.2
B. D. No. 59522‡ ♀ 49 years	3/12/36	160.0	46.7	1.46	180	- 2	82.0	2.20	1.51	46	48	148.6
S. C. No. 69400‡ ♀ 39 years	3/23/36	150.1	47.1	1.41	166	- 4	67.8	2.45	1.74	64	38	153.6
C. C. No. 75892 ♀ 44 years	10/25/34	162.5	46.8	1.47	218	+22	125.6	1.74	1.18	142	12	136.1

*In this column the following abbreviations are used:
Rh. = rheumatic fever
hypt. = hypertension
M.S. = mitral stenosis
M.I. = mitral insufficiency
E.H. = enlargement of heart
sl. = slight

†0, +, ±, ↓, ↑, = absent, present, doubtful, decreased, increased, respectively.

‡This patient, unlike the others in this group, was under the influence of digitalis when the special studies of the circulation were made.

order was the same. It is apparent that the presence of these valve lesions usually decreases the capacity of the heart to pump blood, but A. I. seems to have a beneficial influence on M. S., M. I. and results in less impairment of the circulation than is found in M. S., M. I. alone. There is a notion that the development of hypertension in a

IV

CIENCY AFTER RECOVERY FROM AND DURING CONGESTIVE HEART FAILURE

CARDIAC VOLUME (C.C.)	ARTERIAL PRESSURE (MM. HG)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM.)	VITAL CAPACITY (C.C.)	LEFT VENTRICULAR WORK (GM.M. PER BEAT)	STROKE VOLUME PER KG. (C.C.)	LEFT VENTRICULAR WORK PER BEAT PER KG. (GM. M.)	DIAGNOSIS*	EVIDENCE OF CONGESTIVE HEART FAILURE†				
									DYSPNEA	CYANOSIS	RALES	LIVER	EDEMA
HEART FAILURE													
Rhythm													
1528	114/76	42.6	18.1	3200	39.0	0.46	0.60	Rh., M.S. & M.I., E.H.	0	+	+	+	0
1317	110/80	27.0	17.0	1500	31.0	0.45	0.58	Rh., M.S. & M.I., E.H.	+	+	+	+	+
1579	94/70	26.6	5.8	2700	29.0	0.63	0.65	Rh., M.S. & M.I., E.H.	+	+	0	+	0
Fibrillation													
1019	150-130/90	25.4	23.2	2600	43.8	0.52	0.81	Unk., M.S. & M.I., E.H.	+	+	+	+	+
1399	120-110/74	22.5	6.6	2750	31.3	0.38	0.52	Rh., M.S. & M.I., E.H.	+	+	0	+	+
1320	170/100	34.0	11.4	1550	36.7	0.30	0.55	Rh., M.S. & M.I., hypt., E.H.	0	+	+	+	+
965	110/90	24.0	7.9	1750	36.7	0.54	0.74	Rh., M.S. & M.I., E.H.	0	+	+	+	0
1554	140/80	-	-	2700	40.4	0.45	0.67	Rh., M.S. & M.I., E.H.	+	+	+	+	0
1102	112/70	-	-	2080	19.8	0.30	0.37	Rh., M.S. & M.I., E.H.	0	0	+	+	0
876	122/70	25.4	10.3	2000	62.6	1.03	1.34	Unk., M.S. & M.I., E.H.	+	+	0	+ (ascites)	0
918	108/66	20.2	15.8	2000	45.0	0.81	0.96	Unk., M.S. & M.I., E.H.	+	+	0	+	+
769	150/100	17.0	-	1900	20.7	0.26	0.44	Unk., M.S. & M.I., sl. E.H.	±	+	0	0	0

patient suffering from M. S., M. I. exerts a beneficial effect,[12, 13] probably due to dilatation and enlargement of the left ventricle and stretching of the mitral ring. A. I. may perform a similar function. On the other hand, the combination of A. S. and A. I., or their addition to M. S., M. I., exerts a very unfavorable effect on the circulation. Organic M. I. may result in decrease in functional capacity, but M. S., A. S., and A. I. are not individually incompatible with average circulatory function. In patients with valve lesions who had not had failure, the circulation time did not show any marked change except in the M. S., M. I., A. S., A. I. group.

TABLE

NAME, HISTORY NUMBER, SEX, AGE	DATE	HEIGHT (CM.)	WEIGHT (KG.)	BODY SURFACE (SQ. M.)	OXYGEN CONSUMPTION (C.C. PER MIN.)	BASAL METABOLIC RATE (%)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC OUTPUT (LITERS PER SQ. M. PER MIN.)	HEART RATE (PER MIN.)	STROKE VOLUME (C.C.)	CARDIAC AREA (SQ. CM.)
RECOVERED FROM CON												
Normal												
S. S. ♂ No. 123829 32 years	2/24/36	166.2	60.7	1.68	236	- 1	74.3	3.20	1.90	58	55	172.9
W. B. ♀ No.131257 32 years	5/ 7/36	151.0	46.0	1.39	166	- 4	82.3	2.02	1.50	48	42	183.4
F. S. ♂ No. 89187 24 years	4/13/35	172.5	49.4	1.58	195	-11	64.6	3.02	1.91	72	42	162.9
M. R. ♀ No. 60143 32 years	4/ 4/34	149.0	52.2	1.45	158	-12	89.6	1.76	1.21	60	29	154.4
C. W. ♂ No. 88345 25 years	12/ 7/35	183.2	71.0	1.92	290	+ 6	73.4	4.00	2.03	70	57	273.6
	12/19/35	184.5	70.8	1.94	286	+ 6	75.8	3.77	1.95	70	54	273.2
L. A. ♀ No. 7210 24 years	5/11/34	162.5	56.0	1.60	179	-12	68.6	2.61	1.64	70	37	140.6
	5/31/34	163.0	57.9	1.64	194	- 8	65.5	2.95	1.80	93	32	137.7
Auricular												
J. G. ♂ No. 16102 28 years	3/25/35	162.7	48.0	1.50	247	+18	74.1	3.33	2.22	60	56	146.5
J. G. ♂ No. 16102 28 years	11/12/35	162.5	52.3	1.55	237	+ 9	86.3	2.75	1.80	66	42	154.3
	11/16/35	153.2	51.5	1.55	226	+ 5	86.2	2.61	1.70	50	52	143.5
L. C. ♀ No. 36623 30 years	3/ 6/35	165.0	60.3	1.66	207	0	74.4	2.78	1.70	70	40	185.3
M. C. ♀ No. 119155 53 years	2/14/36	148.0	65.8	1.60	193	+ 6	77.8	2.48	1.55	70	35	168.7
G. MacF. ♂ No. 124205 57 years	2/29/36	163.3	48.9	1.51	182	- 5	70.8	2.57	1.70	68	38	143.1
M. P. ♀ No. 62815 41 years	5/10/34	160.5	51.5	1.53	159	-17	74.3	2.14	1.40	59	36	162.0
M. R. ♀ No. 19718 25 years	4/11/34	164.8	48.9	1.52	191	- 2	96.2	1.98	1.30	86	23	189.8
	4/20/34	165.7	47.7	1.52	180	0	98.2	1.83	1.20	106	17	194.4
J. W. ♂ No. 28813 28 years	3/ 9/34	163.8	50.2	1.53	188	-10	92.0	2.05	1.34	74	28	-
	3/12/34	163.6	50.3	1.53	171	-18	88.0	1.95	1.27	69	29	-

The patient with coaretation of the aorta* was included because of the functional similarity of this lesion to aortic stenosis. There was also evidence of slight aortic insufficiency. The patient at the time of our examination had no clinical evidence of cardiac insufficiency. Nevertheless, marked changes in the circulation had occurred in the year since Grollman and Ferrigan[14] had studied him. The arteriovenous oxygen difference had increased from 61.0 c.c. to 90.3 c.c., and the cardiac output per minute had decreased from 4.90 liters to

*Earlier observations on this patient were reported by Grollman and Ferrigan[11].

IV—CONT'D

CARDIAC VOLUME (C.C.)	ARTERIAL PRESSURE (MM. HG)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM.)	VITAL CAPACITY (C.C.)	LEFT VENTRICULAR WORK (GM.M. PER BEAT)	STROKE VOLUME PER KG. (C.C.)	LEFT VENTRICULAR WORK PER BEAT PER KG. (GM. M.)	DIAGNOSIS*	EVIDENCE OF CONGESTIVE HEART FAILURE†				
									DYSPNEA	CYANOSIS	RALES	LIVER	EDEMA
GESTIVE HEART FAILURE													
Rhythm													
1097	105/58	31.7	5.8	3450	61.0	0.91	1.00	Rh., M.S. & M.I., E.H.	0	0	0	+	0
1198	98/65	24.0	5.3	2100	47.0	0.91	1.02	Rh., M.S. & M.I., E.H.	0	0	0	0	0
1005	106/66	11.5	9.5	4400	49.0	0.85	0.99	Rh., M.S. & M.I., E.H.	0	0	0	0	0
925	115/55	-	-	2100	34.0	0.56	0.65	Unk., M.S. & M.I., E.H.	±	+	0	0	±
2185	102/54	24.0	10.5	3850	60.5	0.80	0.85	Unk., M.S. & M.I., E.H.	0	0	0	0	0
2185	116/66	25.2	8.8	4100	66.8	0.79	0.94		+	0	0	0	0
806	95/60	-	-	2700	39.2	0.66	0.70	Rh., M.S. & M.I., E.H.	±	±	±	±	±
781	120/84	-	-	2610	44.4	0.88	0.77		±	±	±	±	±
Fibrillation													
856	134/65	19.5	8.1	3250	76.2	1.17	1.59	Unk., M.S. & M.I., E.H.	0	0	0	0	0
926	135/76	19.9	9.1	2750	60.5	0.80	1.16	Unk., M.S. & M.I., E.H.	0	+	0	+	0
821	152/76	22.1	6.3	2900	80.6	1.01	1.57		0	+	0	+	0
1218	118-110/74	20.2	6.4	2700	53.9	0.66	0.90	Rh., M.S. & M.I., E.H.	0	0	0	±	0
1160	150/70	22.2	8.1	2000	52.3	0.53	0.79	Rh., M.S. & M.I., hypt., E.H.	0	0	0	0	0
827	118/62	19.7	2.9	1850	46.5	0.78	0.95	Rh., M.S. & M.I., E.H.	0	0	±	0	0
996	100/70	-	-	2200	41.6	0.70	0.81	Rh., M.S. & M.I., E.H.	0	0	↓	↓	0
1271	98/60	-	-	2100	24.7	0.47	0.51	Rh., M.S. & M.I., E.H.	±	±	±	±	±
1310	98/60	-	-	2310	18.5	0.36	0.39		±	±	±	±	±
-	115/80	-	-	2400	37.3	0.56	0.74	Unk., M.S. & M.I.	±	±	±	±	±
-	115/80	-	-	2270	38.7	0.58	0.77		±	±	±	±	±

3.52 liters, the cardiac index from 2.50 liters to 1.93 liters, and the stroke volume from 60 c.c. to 41 c.c. The basal systolic blood pressure had risen, and the diastolic had fallen. The heart was greatly enlarged, and the work per beat was not commensurate with its great size (see p. 498). The patient died of pneumonia one month after our observations were made.

In comparing the observations made on the M. S., M. I. groups before the occurrence of failure, during failure, and after recovery from failure, certain differences were found. There were marked impair-

TABLE V

MEAN VALUES OF MEASUREMENTS OF NORMAL INDIVIDUALS,* AND OF PATIENTS WITH MITRAL STENOSIS AND INSUFFICIENCY, BEFORE FAILURE, RECOVERED FAILURE AND DURING FAILURE (TABLE IV)

	ARTERIO-VENOUS OXYGEN DIFFERENCE (C.C.)	CARDIAC INDEX (LITERS PER MIN.)	STROKE VOLUME (C.C.)	STROKE VOLUME (C.C. PER KG.)	LEFT VENTRICULAR WORK PER BEAT PER KG. (GM. M.)	VENOUS PRESSURE (CM. PHYSIOLOGIC SALINE)	CIRCULATION TIME (SEC.)
Normal Individuals	61.4	2.11	57	0.82	1.04	10.0	14.4
M.S. M.I. Before Failure	71.2	1.86	44	0.70	0.88	9.8	13.2
M.S. M.I. Recovered Failure N.R.	74.0	1.71	51	0.88	0.87	8.0	23.3
M.S. M.I. Recovered Failure A.F.	83.2	1.60	37	0.69	0.93	6.8	20.6
M.S. M.I. Recovered Failure N.R. & A.F.	79.5	1.64	43	0.74	0.90	7.3	21.8
M.S. M.I. During Failure N.R.	105.0	1.49	27	0.51	0.61	13.9	32.1
M.S. M.I. During Failure A.F.	94.0	1.42	27	0.51	0.79	12.5	24.1
M.S. M.I. During Failure N.R. & A.F.	96.6	1.44	27	0.51	0.74	13.0	26.5

*Data from Stewart and Watson.[6]

ment of function when heart failure supervened and improvement with the return of compensation, but the improvement was not sufficient to restore the prefailure level of function; in short, those who recovered from failure took an intermediary position between those who had not experienced failure and those who were suffering from it. Analysis of the data shows that there is progressive increase in arteriovenous oxygen difference and progressive decrease in cardiac index and stroke volume in going from the "no failure" group, to the "recovered failure" group, to the "during failure" group. The circulation time was prolonged during, and after, recovery from failure, but the venous pressure was elevated during failure only. In other words, the heart which is the seat of mitral stenosis and insufficiency is a less effective pump, and blood moves more slowly, when congestive failure is present than before it occurred. With recovery from failure the functional capacity impoves, but the work of the heart per beat is no longer commensurate with its size. The stroke volume per kilogram and left ventricular work per beat per kilogram were slightly greater after recovery from congestive heart failure than before it occurred. This is probably an effect of digitalis, as will be shown in other reports.[2, 5] Because of alterations in heart size as a consequence of failure, the giving of digitalis, even though it decreases the size of the heart and increases the amount of work it can do, does not restore normal circulatory efficiency. It appears from this analysis as well as from other observations which we have made[1, 2, 5] that heart failure is associated with decrease in cardiac output, slowing of the velocity of blood flow, dilatation of the heart, and decrease in the work of the heart per beat so that it is no longer commensurate with the heart size (see p. 498). In short, in heart failure of the congestive type the heart fails to pump an adequate amount of blood. The figures which we have discussed are averages, and it is seen from the frequency charts that there is overlapping. A certain level of output does not correspond to a given degree of failure in all cases, but this is only to be expected with differing degrees of valvular and myocardial damage and individual variations in the adjustments of the circulatory system and of the whole organism. Although, in general, the conclusions of McGuire, Hauenstein, and Shore[15] are in agreement with ours, theirs do not appear to be based on adequate data. In the first place, they state that "at the time of the determinations of the cardiac output, varying degrees of improvement in symptoms and physical findings had resulted from rest, the administration of digitalis and other therapeutic procedures." Moreover, they include observations relating to pericarditis with effusion. Obstruction to the flow of blood into the heart is quite different from failure of the heart per se.[16] Since their experiments were designed to compare the direct

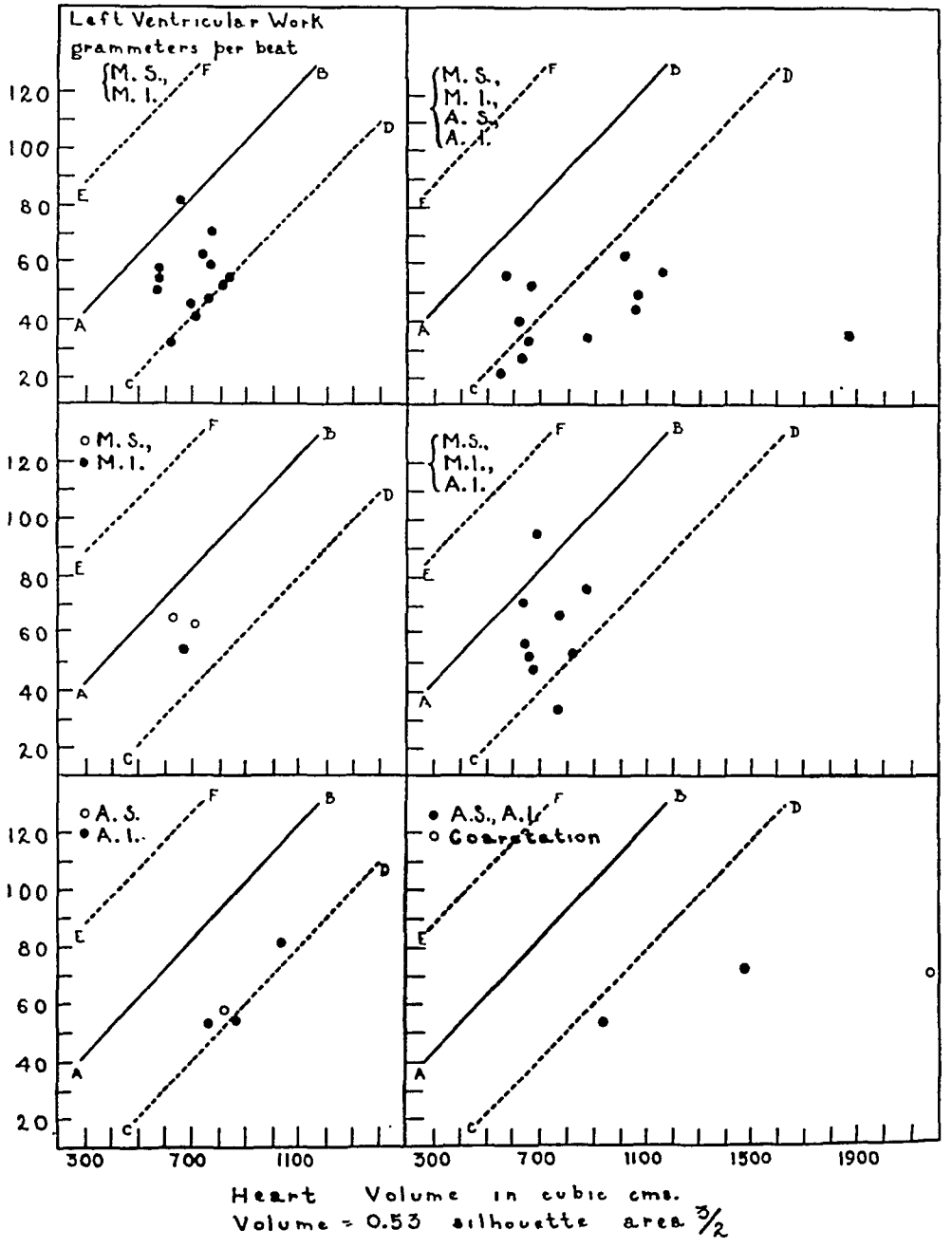

Fig. 3.—Left ventricular work per beat and cardiac volume. The data from Tables II and III relating to work of the left ventricle per beat in the presence of valve lesions are plotted against the corresponding cardiac volumes. Line *AB* represents the best line, the regression of the work on area, defined by Starr, Collins, and Wood on the basis of a statistical treatment of data from a control group of cases. Lines *CD* and *EF* are placed by these authors at a distance of twice the standard deviation from *AB*. It appears from their observations that a patient falling within zone *CD-EF* has a normal circulatory function. That is to say, the work of the heart is commensurate with its size; on the other hand, they found that the values relating to patients who had suffered from cardiac decompensation fell in a zone below *CD*. Each closed or open circle represents a measurement in that valve group as indicated. It is apparent that A.S., A.I., M.S., M.I., and M.S., M.I., lie within the zone *CD-EF* or at the border line *CD*; but A.S., A.I., coarctation, M.S., M.I., A.I., and M.S., A.S., A.I., begin to fall outside the zone of normal circulatory function.

Fick method with the acetylene method, closer correlations would probably have prevailed if comparative measurements had been carried out on the same day, in accordance with the principles established by Baumann and Grollman,[17] rather than at forty-eight-hour intervals.

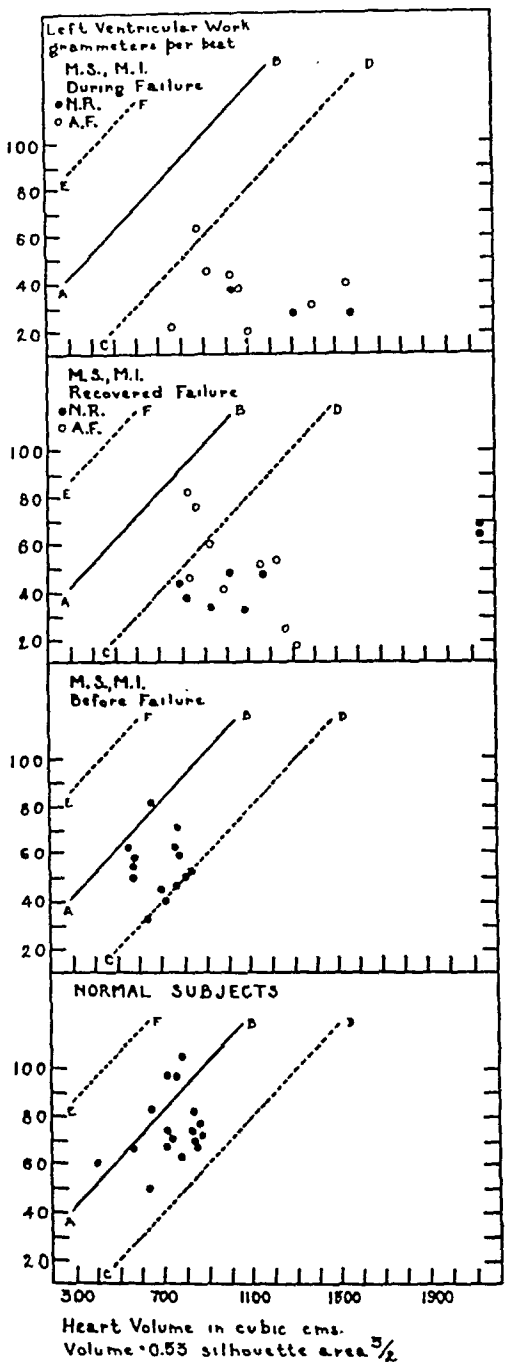

Fig. 4.—Left ventricular work per beat and cardiac volume. The data of Tables IV and V relating to work of the left ventricle per beat are plotted against cardiac volume in normal subjects, in M.S., M.I. before failure, in M.S., M.I. after recovery from failure, and in M.S., M.I. during failure, in a manner similar to Fig. 3. Most of those recovered from failure and during failure fell outside the zone *CD-EF*, but those during failure were for the most part lower and farther away from line *CD*.

The work of the left ventricle per beat has been plotted against the cardiac volume (Fig. 3). Stewart and Cohn[1] suggested that Starling's law[18] of the heart is applicable to human beings with heart failure and that the changes associated with the use of digitalis are subject to interpretation on this basis. Starr and his associates, in a statistical analysis, have shown that in the presence of normal circulatory function the work of the left ventricle per beat is proportional to the size of the heart.[4, 19] From their data they have defined a zone of normal circulatory function. In those falling below their line *CD* the work per beat is not commensurate with the heart size, and patients suffering from congestive heart failure have been found to lie in this area (Starr,[4, 19] Stewart[2, 5]). Work may be calculated by making use of the formula[20] $W = QR + \frac{wV^2}{2g}$, in which W equals work done per beat, Q equals stroke volume, R equals mean arterial blood pressure in mm. Hg × 13.6, V equals velocity of blood at aorta, w equals weight of blood, and g equals acceleration due to gravity. The last part of the formula $\frac{(wV^2)}{(2g)}$ has been omitted.

With single lesions (aortic stenosis, or aortic insufficiency, or mitral stenosis, or mitral insufficiency) the work done may be commensurate with the size of the heart. Also, in the cases of mitral stenosis and insufficiency all observations lie inside or just at the border of the normal zone *CD-EF* (Fig. 3). In the cases of mitral stenosis and insufficiency and aortic insufficiency, only one observation lies outside the normal zone below line *CD*. In aortic stenosis and aortic insufficiency and coarctation the observations lie in the heart failure zone below *CD*, and in mitral stenosis and insufficiency and aortic stenosis and insufficiency only 3 observations lie in the normal zone *CD-EF*, showing that in 10 instances the work done by the left ventricle was not commensurate with the cardiac size. It appears that aortic stenosis when combined with other lesions results in enlargement out of proportion to the work which the heart can do.

The work relationships for the mitral stenosis and insufficiency groups have been studied. As has already been shown, before the occurrence of failure the left ventricular work per beat may be commensurate with the size of the heart, which places the cases in the normal zone *(CD-EF)*, but for the most part below the best line *AB* (Fig. 4). Of the observations made on these patients after they had recovered from congestive heart failure, two lie in the normal zone and all the others in the heart failure zone. Only one observation made during failure was in the normal zone; all the others lay outside below line *CD*, and farther away from it than those on the patients

who had recovered from failure. In short, the disproportion between work per beat and the size of the heart becomes greater during failure and is not entirely abolished after recovery from failure.

It is likely that the deficiencies which have been demonstrated with the patients in the basal state attain greater proportions when they are active.

CONCLUSION

Valve lesions result in certain defects in the functional capacity of the heart which can be detected before failure is apparent clinically. Single lesions are not incompatible with a fairly normal circulation at rest, but in all instances in which there is more than one lesion functional alterations appear. Aortic stenosis in combination with other lesions results in marked decrease in function. The order of magnitude of the functional defect increased progressively in going from the M. S., M. I., A. I. group to the M. S., M. I. group, to the M. S., M. I., A. S., A. I. group. It is inferred that aortic insufficiency is of functional benefit when superimposed upon M. S., M. I. Patients suffering from M. S., M. I., A. S., A. I. exhibit the most marked alterations. Aortic stenosis results in so much enlargement of the heart that when combined with other lesions the work per beat no longer is commensurate with the size of the organ.

When patients with mitral stenosis and insufficiency suffer failure, all of the measurements of the circulation which we made become subnormal, i.e., the arteriovenous oxygen difference increases, the cardiac index decreases, the circulation time increases, the venous pressure rises, and the work is no longer commensurate with the size of the heart. When they recover from heart failure the functional capacity increases, but usually does not regain its prefailure level.

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Department of Clinical Reports

RIGHT-SIDED PLEURAL EFFUSION IN HEART FAILURE*

Report of an Unusual Case

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THE following case is reported in order to attract attention to the fact that right-sided pleural effusion may dominate the picture of heart failure to such a degree that there is difficulty in making a correct etiological diagnosis. The number of aspirations and the total amount of fluid removed are also unique and noteworthy. Furthermore, the pathologic findings are interesting, clear-cut, and definitely indicate that the peculiar clinical manifestations were due to heart failure.

Case Report.—F. Z., a 53-year-old white American male, entered the Cleveland City Hospital, June 24, 1936. His chief complaint was breathlessness. The patient said that he had been in excellent health until Feb. 3, 1936 (about four and one-half months before admission), when he suddenly developed rather marked shortness of breath and slight pain in the precordial region. The pain disappeared shortly, but thereafter the patient had had progressively severe shortness of breath on exertion, weakness, a twenty-pound weight loss, lassitude, and cough productive of mucus.

Examination showed the patient to be normally developed, chronically ill, and moderately dyspneic. The fundi showed slight arteriolar sclerosis. The anteroposterior diameter of the chest was greater than normal. There were signs of fluid in the right pleural space. The heart was enlarged and showed tachycardia and an apical systolic murmur. The blood pressure was 114/80. It was specifically noted that the patient did not have distention of the jugular veins, an enlarged tender liver, or edema of the legs or sacral region.

Urinalysis on numerous occasions gave negative results. The value for the hemoglobin was 70 per cent; the erythrocytes numbered 3,150,000 and the leucocytes 8,400 per cubic millimeter. The value for blood urea nitrogen was 16.8 mg. per 100 c.c. The value for the total serum nitrogen was found to be 815 mg. per 100 c.c., for total serum protein 4.9 gm. per 100 c.c., for serum albumin 2.5 gm. per 100 c.c., and for serum globulin 2.4 gm. per 100 c.c. The albumin-globulin ratio was 1.05. The Kline test for syphilis was negative.

Fluoroscopic and roentgenographic studies of the chest showed the heart to be enlarged in its transverse diameter. The cardiac configuration was of the aortic type. There was cloudiness at the right base due to the presence of fluid. The lung markings were increased in density throughout both lung fields.

The electrocardiogram in the conventional leads showed splintered Q-waves in Leads II and III. The T-wave in Lead III was negative (inverted). Lead IV (made with one electrode at the apex and the indifferent one on the left leg) revealed a positive (upright) T-wave.

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Bronchoscopy, which was done on June 27, 1936, revealed no abnormalities.

On admission, thoracentesis on the right yielded 1,000 c.c. of serosanguineous fluid. This fluid in the right pleural space reaccumulated almost immediately. Between June 24, 1936, and Sept. 21, 1936, a period of ninety days, thoracentesis was performed forty-five times. The total amount obtained was 47,925 c.c., or an average of 1,065 c.c. on each occasion. For one period of nineteen consecutive days thoracentesis was performed once each day, with removal of 1,000 c.c. every time. The fluid varied in character, being serous or serosanguineous. The specific gravity originally was 1.020, but gradually dropped to between 1.012 and 1.015. Cultures of the fluid for pyogenic organisms showed no growth. The fluid was injected into a guinea pig, which failed to develop tuberculosis. Tumor cells were not present in the aspirated material.

During this period the patient's general condition remained much the same. He showed a constant tachycardia and more or less breathlessness. Fluid never accumulated in the left pleural space to any degree nor did the patient show any more than very slight edema of the feet or sacral region. After Sept. 21, 1936, the patient improved very slowly and thoracentesis was no longer necessary, although the patient did require salyrgan periodically. Recovery, however, was very slow and it was not until June 15, 1937 (almost one year after admission) that the patient was discharged.

The patient got along fairly well thereafter until October, 1937, when he developed severe dyspnea and weakness. At this time his private physician aspirated the right pleural space and obtained 300 c.c. of serous fluid. The patient became steadily worse, however, and was readmitted to the hospital Nov. 2, 1937. The findings were much as before except that the cardiac mechanism was now auricular fibrillation. The right pleural space again contained fluid. There was no edema of the legs. Thoracentesis was performed twice with removal of 500 c.c. of serosanguineous fluid on each occasion. The specific gravity was 1.012. The patient's condition became progressively worse despite all treatment, and he died Nov. 11, 1937.

The diagnoses were: (1) Coronary artery disease; (2) coronary thrombosis, remote, with old myocardial infarct; (3) cardiac hypertrophy and dilatation; (4) myocardial insufficiency; (5) auricular fibrillation; (6) right-sided pleural effusion.

Autopsy.—The autopsy was performed two hours after death. External examination was negative. On section there was no ascites or peritonitis, and no hydrothorax on the left. The right lung showed marked atelectasis. The right pleural space was completely obliterated by fibrous adhesions except for a space above the diaphragm 8 cm. in length. This cavity did not contain fluid. The wall was formed by fibrous tissue covered by a small amount of dried blood. There was no evidence of tuberculosis or tumor.

The heart was markedly enlarged in all directions and weighed 725 gm. The parietal pericardium was adherent to the epicardium over the dorsal aspect of the left ventricle and in the region of the pulmonary conus. The right atrium was dilated and the right auricular appendage contained several large pre-mortem thrombi which were adherent to the wall. The tricuspid valve was normal. The right ventricle showed hypertrophy and dilatation. The pulmonic valve was normal.

The left atrium was dilated; the mitral valve showed slight thickening. One chorda tendinea of the posterior papillary muscle was ruptured. The left ventricle showed hypertrophy and dilatation, with moderate fibrosis of the myocardium. The posterior wall of the left ventricle was the seat of a saccular aneurysm, the opening of which measured 4.5 by 3.5 cm. and the depth of which was 2.5 cm. The wall of this aneurysm bulged posteriorly and consisted of glistening, white fibrous tissue partially covered by friable pinkish-gray thrombi.

The right coronary artery showed moderate to severe arteriosclerosis with reduction of its lumen in some places to one-third of the normal size, but it was not actually occluded. The left coronary artery showed a similar degree of sclerosis, and, in addition, the left circumflex branch was completely occluded save in its proximal 2 cm. This occluded artery led directly into the area occupied by the cardiac aneurysm.

The left lung showed passive hyperemia and emphysema. The right lung was markedly reduced in size, atelectatic, and moderately emphysematous; the pleura was uniformly thickened; and almost the entire moddle lobe was the seat of infarction. The lower lobe contained an infarct which measured 3 by 1 cm. in its greatest diameter. The main branch of the right pulmonary artery was practically occluded by a laminated pre-mortem thrombus which extended into the tributaries leading to the right middle and right lower lobes. The pulmonary arteries showed moderately severe arteriosclerosis.

The kidneys showed slight arterial and arteriolar nephrosclerosis. The remaining organs showed passive hyperemia but no other important abnormality to macroscopic examination.

Microscopic examination of the aneurysm of the left ventricle showed that the wall was made up largely of dense fibrous connective tissue with only an occasional hypertrophied muscle cell. The parietal pericardium was adherent to the epicardium and contained numerous large blood vessels. The aneurysm was lined by a partially organized mural thrombus.

A section of the left circumflex coronary artery showed severe arteriosclerosis and complete fibrous occlusion of the lumen with one to three small channels of canalization.

Microscopically, the middle and lower lobes of the right lung showed atelectasis, emphysema, and infarction. The arteries showed moderate arteriosclerosis. The pleura on the right was thickened and fibrous, with no evidence of acute or chronic inflammation, tuberculosis or tumor. The remaining viscera showed passive hyperemia.

The autopsy diagnoses were: (1) Coronary arteriosclerosis, severe, with occlusion (old) of left circumflex coronary artery; (2) saccular aneurysm of posterior wall of left ventricle near base; (3) cardiac hypertrophy and dilatation (725 gm.); (4) embolism and infarction of right lung; (5) mural thrombosis of right auricular appendage and left ventricle; (6) rupture of chorda tendinea to posterior papillary muscle; (7) chronic adhesive pericarditis, localized; (8) induration collapse of right lung; (9) fibrosis of myocardium of left ventricle; (10) chronic passive hyperemia of liver, spleen, and kidneys; (11) pulmonary emphysema; (12) pulmonary arteriosclerosis, moderately severe; (13) arterial and arteriolar nephrosclerosis, slight.

COMMENT

It has been known for a long time that heart failure causes effusions in the right pleural space more often than in the left.* This case is remarkable, however, in the degree to which right pleural effusion dominated the picture of heart failure. Forty-five aspirations of the right pleural space were done in ninety days, and an average of 1,065 c.c. was removed on each occasion. It is to be noted that for all practical purposes the fluid accumulated in the right pleural space only. Even

*Dock, W.: The Anatomical and Hydrostatic Basis of Orthopnea and of Right Hydrothorax in Cardiac Failure, AM. HEART J. 10: 1047, 1935.

terminally the patient had very slight edema and he never had ascites or a left-sided hydrothorax of any consequence. In fact, the only other significant signs of myocardial insufficiency were breathlessness and tachycardia, and these originally were ascribed to the pleural effusion.

This case accordingly illustrates that at least in its earlier stages heart failure may be evidenced by pleural effusion alone. Fluid in the pleural space under such circumstances raises a problem in differential diagnosis. In this instance the rapid accumulation of this fluid led to an original diagnosis of carcinoma metastatic to the pleura, and the heart disease was considered to be incidental. This possibility was rendered more likely by the fact that the pleural fluid was serosanguineous and had a specific gravity of 1.020. It was this incorrect diagnosis of carcinoma that led to the performance of bronchoscopy. In fact, only upon continued observation and investigation was carcinoma ruled out as a cause of the accumulation of the fluid. It has been noted that the specific gravity gradually decreased until it was that of a transudate (1.012 to 1.015). Whether these changes in specific gravity were significant is not known.

At autopsy, the pleural space on the right was small, and aspiration shortly before death yielded only 500 c.c. of fluid. This was in marked contrast to the amounts obtained only a little over one year prior to death (on one occasion 1,850 c.c. were removed). Evidently the long-standing pleural effusion had led to a sterile pleuritis with the development of pleural adhesions.

The heart was greatly hypertrophied (725 gm.). There are no data as to whether the patient had hypertension at an earlier date, but during the last one and one-half years of his life the blood pressure was always normal. Anatomically, definite evidence of chronic hypertension was lacking. The patient did have severe coronary artery disease with occlusion of the left circumflex branch which resulted in a myocardial infarct at the base of the left ventricle. There was electrocardiographic evidence of this infarct one and one-half years prior to death, and the history indicates that it occurred almost two years before death. A focal pericarditis and a saccular aneurysm had developed at the site of infarction.

These cardiac findings and the presence of severe chronic passive hyperemia of the parenchymatous organs constitute anatomic evidence that the heart had been inadequate for a long time. The sequence of clinical events resulting in death can unquestionably be regarded as being due to cardiac failure.

CHOLESTEROL PERICARDITIS*

Report of a Case

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CHOLESTEROL pericarditis is an entity unknown in the English literature. Only a few cases have been reported, all of which appeared in the German literature. The following case is reported because of the rarity of this condition, the remarkable response to treatment, and the possibility that it represents an unusual myxedematous syndrome with an elevated basal metabolic rate.

CASE REPORT

Mrs. L. M., a 54-year-old white woman, was admitted to the Vanderbilt University Hospital Feb. 17, 1937, and discharged March 3, 1937. Her general health had always been good, and her past history was not remarkable save for one miscarriage (of a four-month-old fetus) after bearing four normal children at term. She denied having venereal disease, and there was no family history of tuberculosis. Her mother, who is living, has diabetes mellitus.

A relative stated that the patient had had dyspnea on exertion and dependent edema for eight years, but the patient herself first became aware of her dyspnea in the spring of 1934. This progressed gradually until September, 1936, when she began to have mild attacks of vertigo, slight dyspnea at rest, dependent edema, and swelling of her abdomen. She consulted her family physician who told her that she had hypertensive heart disease and sent her to a hospital where she improved moderately on a regime of digitalis, diuretics, and bed rest. She continued to have dyspnea after discharge and for eleven weeks spent most of her time in bed, during which period her edema and ascites progressed, and she became markedly orthopneic. In October, 1936, she was again treated in the hospital, with little relief. Within the next four months all signs of decompensation became more marked, and early in February, 1937, an abdominal paracentesis was performed. Five liters of clear, straw-colored fluid were removed, after which her dyspnea was relieved for three days, but it returned so rapidly that she was sent to the Vanderbilt Hospital for study and treatment under the direction of Dr. Tinsley Harrison. She had never been unduly susceptible to cold weather, but had noticed that her voice had become more masculine and her skin somewhat drier during the three years previous to admission.

On physical examination her skin was dry, rough, and pale, her voice was low pitched and husky, her features were coarse, and the lateral portion of her eyebrows very thin. Her hair, however, was of normal luxuriance. The heart sounds were distant, but there was no murmur, friction rub, or gallop. The pulse rate was 72 per minute, and the cardiac rhythm was normal. A moderate number of congestive râles were present at both lung bases, more in the left. Very little sclerosis of the peripheral vessels was noted. The arterial pressure, which was 240/140, varied

*From the Department of Medicine, Vanderbilt University.
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TABLE I

	DATE														
	2/17	2/18*	2/19*†	2/20	2/21	2/22	2/23	2/24	2/25	2/26	2/27	2/28	3/1	3/2	3/3
Weight (lb.)	185	186½	177½	172½	170	158	153½	155	153½	151	151	148½	147½	146	146
Blood pressure		210/120	160/90	135/60			140/80	160/80	160/80	140/80					
Basal metabolic rate						Plus 19	Plus 20							Plus 39	
Medicinal preparations		Theocin Salyrgan	Thyroid started		Salyrgan	Theocin									

*Karell diet.
†Pericardial tap.

between inspiration and expiration through a range of 15 mm., but the pulse was not definitely paradoxical. The ascites prevented satisfactory palpation of the liver. Fluoroscopic examination revealed a high diaphragm and a cardiac shadow which was tremendously enlarged to the right and left. There was some increase in the width of the shadow at the base when the patient assumed the recumbent posture.

The following day, 500 c.c. of satiny, opalescent fluid were removed from the pericardial sac by the right thoracic approach. The specific gravity was 1.020 (corrected for temperature), and there were 75 cells per cubic millimeter, chiefly lymphocytes and erythrocytes. Culture showed a gram-positive bacillus after nineteen days which could not be identified (contaminant?), and the guinea pig which was inoculated did not develop tuberculosis after three months. Microscopically, the fluid was found to contain innumerable cholesterin crystals. A quantitative determination of the cholesterol content was not done, but similar fluids described in the literature on cholesterol pleural effusions were found to contain approximately 2000 mg. per cent. The blood cholesterol was 278 mg. per cent. The patient was greatly improved symptomatically after the tap; her arterial pressure fell from 250/115 to 130/65, but she was still in a critical condition. Because of her myxedematous appearance, low-pitched voice, and high blood cholesterol, it was decided to give her ½ grain of desiccated thyroid gland twice a day in spite of the basal metabolic rate of plus 19 (corrected for edema). Table I summarizes the patient's subsequent course; she improved rapidly during the remainder of her stay.

Repeated examinations of the urine showed nothing remarkable save for a small amount of albumin. The erythrocyte and total and differential leucocyte counts were within normal limits, and the hemoglobin was 11.5 gm. per 100 c.c. of blood. The sugar and nonprotein nitrogen content of the blood were normal. Electrocardiograms showed low voltage in all leads, and one record revealed paroxysmal auricular tachycardia.

The patient was not seen again until July 7, 1937, when she stated that she had discontinued her digitalis and thyroid extract one month previously. She agreed to return for study two weeks later, and was instructed to resume thyroid extract, which she took for only one week because of rapid loss of weight. When she returned she felt less nervous than she had for several years and, although she was somewhat weak, she had experienced no dyspnea, edema, or precordial pain. Her weight was only 115 pounds. The lungs presented no evidence of congestion, and there was no enlargement of the liver and no edema. Her voice had a normal pitch. The heart was still markedly enlarged to the left and moderately to the right. Fluoroscopic and physical examinations gave no evidence of pericardial effusion. The arterial pressure was 230/120. The blood cholesterol was 263 mg. per cent, and the basal metabolic rate +6 per cent.

Of the reports of cases of cholesterol pericarditis, only that of Dániel and Puder[1] was accessible. Their patient at autopsy showed lesions in the lung and pericardial sac which were thought to be both syphilitic and tuberculous. The patient's Wassermann was positive, and tubercle bacilli were found in the tissues. However, spirochetes could not be demonstrated and the entire microscopic picture was compatible with that of tuberculosis alone. The authors mentioned one interesting hypothesis in attempting to explain the presence of cholesterol in the pericardial fluid. They thought that originally the patient might have had

hemopericardium, with subsequent hemolysis of the erythrocytes, absorption of part of the fluid, and precipitation of the cholesterol which had been present in the bloody fluid.

We are at a loss to explain the etiology in our case. Even if the patient had definite myxedema, the latter would not account for the cholesterol in the pericardial fluid, for in none of the reported cases of myxedematous pericardial effusion were cholesterol crystals found in the effusion. Although the negative result of the guinea pig inoculation does not rule out tuberculosis, it certainly makes it less likely. Whether or not a bloody effusion might have been present originally cannot be said, but there were very few erythrocytes in the fluid at the time of the tap.

Another feature of this case about which we may speculate is the possibility that the patient had myxedema with an elevated or normal basal metabolic rate. Hurxthal[2] reports several such cases in which there was a favorable response to thyroid extract, and thinks that in the absence of other obvious causes for hypercholesterolemia a patient with this condition should be treated for masked hypothyroidism regardless of the basal metabolic rate. Part of the increase in our patient's oxygen consumption may have been due to her dyspnea, but at the time when the measurements were made none was evident. She was given morphine before the first and second measurements. One should bear in mind that this is merely speculation, as we have no definite evidence that this patient had myxedema.

REFERENCES

1. Dániel, G., and Puder, S.: Perikarditis et Pleuritis Cholesterinea, Virchows Arch. f. path. Anat. 284: 853, 1932.
2. Hurxthal, L. M.: Blood Cholesterol and Thyroid Disease, III. Myxedema and Hypercholesteremia, Arch. Int. Med. 53: 762, 1934.

Department of Reviews and Abstracts

Selected Abstracts

Scupham, George W., Takats, Geza (de), Van Dellen, Theordore R., and Beck, William C.: Vascular Diseases. A Review of Some of the Recent Literature, With a Critical Review of the Surgical Treatment. Arch. Int. Med. 62: 482, 1938.

In the past year the importance of general involvement in the course of vascular diseases has been emphasized by a number of writers. In the association with this idea, primary vascular hypertension has been occupying a larger place in investigative interest. A brief resume of some of the work on this subject is included in this review.

No attempt has been made to discuss all the papers which have been published, but certain ones have been selected which seem to be contributions to the knowledge of vascular diseases. In some instances material has been included which has been covered, at least in part, in previous reviews. This has been done because the subject seems to bear the emphasis of repetition without becoming commonplace.

This annual review contributes a brief analysis of the literature on this subject. It is an important and useful contribution.

AUTHOR.

Kylin, E., and von Koranyi, A.: Studies on Blood Pressure and Blood Sugar in Rabbits Into Which Pituitary Glands Were Transplanted. Klin. Wchnschr. 17: 668, 1938.

Kylin's theory that a certain number of individuals with hypertension and hyperglycemia are suffering from hyperfunction of the pituitary gland is restated and the antithesis between this group of hypertensive patients and Simmond's disease redrawn. The present study concerns the implantation of the pituitary gland of calves into eight rabbits. Within a few days after transplantation, blood pressure rises (from 75 to 100 mm. Hg) and then falls after one or two months. After six months, however, it rises again and remains elevated at a level of 100 to 115 mm., which is equivalent to a pressure of about 220 mm. Hg in man. Concomitantly, the blood sugar rises from a level of 80 or 100 to 146 mg. per cent. The thesis that hypertensive-diabetic syndrome is due to hyperfunction of the pituitary gland receives additional support.

STEELE.

Gollwitzer-Meier, Kl., HaeuBler, H., and Krüger, E.: Effect of Hydrogen Ion Concentration of Blood on Gaseous Exchange of Heart. Arch. f. d. ges. Physiol. 239: 120, 1937.

An increase in pH following carbon dioxide or lactic acid addition to blood of the heart-lung preparation decreases oxygen consumption. A decrease in pH following sodium carbonate increases oxygen consumption. There is an increase

in mechanical efficiency of the heart when the blood becomes acid and a decrease when it becomes alkaline. The effects of pH are independent of diastolic heart size and constitute a deviation from Starling's law.

KATZ.

Meyer, F., and Eckers, H.: The Action of Tyramin Upon the Circulation, According to Studies in Man. Arch. f. exper. Path. u. Pharmakol. 189: 200, 1938.

Tyramin acts on intravenous and subcutaneous injection, but not on oral or rectal administration. The quickness with which the rise in arterial pressure passes off, the exceedingly small effect upon diastolic pressure, and the increase in volume output of the heart are all evidence against the notion that tyramin plays a part in maintaining the high arterial tension in essential hypertension.

STEELE.

Rothschuh, K. E.: Diacapillary Hypertension Due to Stasis. Klin. Wchnschr. 17: 51, 1938.

The author has observed a diastolic arterial hypertension in several patients during periods of congestive heart failure which subsided with recovery. In two examples he shows the regularity with which the level of diastolic arterial pressure follows that of venous pressure. He finds, moreover, that brachial diastolic arterial pressure is on an average 10 mm. Hg higher when the arm is hanging down than when it lies horizontally. This he takes as additional evidence that venous pressure affects diastolic arterial pressure. He concludes, admitting the preliminary nature of this study, that distention of the veins exerts back pressure through capillaries and increases the resistance in the arterioles.

STEELE.

Fasshauer, W., and Oettel, H. J.: A Clinical Contribution on the Variability of Automatic Regulation of the Vasomotor System. Klin. Wchnschr. 17: 620, 1938.

Arterial pressure was followed in fifty-two normal individuals including some well-trained athletes while the position of the body was changed from 45° with the head up, through the horizontal to 45° with the head down on a tip-table. Arterial pressure was followed by means of Lange's apparatus. Three records are shown. The pressure normally falls when the head is raised and rises when it is lowered. When the arterial pressure is raised either by adrenalin, sympatol, or veritol, the changes in pressure which occur with changes in position are abolished. If the drug does not affect the normal level of pressure, then changes in pressure with change in position are not affected.

STEELE.

Linnell, J. W., Thomson, W. A. R.: Some Cardiological Fallacies. Brit. M. J. 2: 442, 1938.

The authors apparently have assumed the truth of the old saying, "Not knowing things does not hurt so much, as knowing so many things that are not so." They discuss briefly many unfounded beliefs regarding cardiovascular disease. The viewpoint is interesting and probably helpful in pointing out the frequency with which these beliefs occur.

MCCULLOCH.

Yater, Wallace M.: Pathogenesis of Bundle Branch Block: Review of the Literature; Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction System. Arch. Int. Med. 62: 1, 1938.

A review of the essential literature concerning bundle branch block has been made.

Sixteen cases of bundle branch block, with necropsy data, have been reported.

Six cases of bundle branch block studied by means of serial sections through the conduction system have been reported.

Bundle branch block is usually due to disease of the coronary arteries, either rheumatic or degenerative, or to hypertension resulting in strain of the left ventricle and impairment of the nutrition of the endocardium and bundle branch.

Bundle branch block is usually associated with bilateral bundle branch lesions, although one branch is usually more seriously affected than the other and probably usually determines the essential form of the electrocardiographic curve.

The newer, or American, terminology is more nearly correct for bundle branch block in man, although it must be admitted that whether right or left is used to modify the diagnosis of this conduction disturbance, the adjective merely indicates the branch more seriously affected.

The uncommon form of bundle branch block, right bundle branch block, is probably usually due to rheumatic arteritis or rheumatic myocarditis.

The common form of bundle branch block, left bundle branch block, is probably due to degenerative cardiovascular renal disease, meaning coronary arteriosclerosis or arterial hypertension, or both.

A bundle branch need not be entirely destroyed at any level in order to produce electrocardiographic alterations that may be designated as typifying bundle branch block.

An increased amplitude of the ventricular complex is not essential to the electrocardiographic diagnosis of bundle branch block.

Any increase of the QRS interval beyond 0.1 second may indicate lesions of the bundle branches.

Many questions remain unanswered in regard to bundle branch block, and many careful histopathologic studies must be made before most of them can be answered.

AUTHOR.

Ruegsegger, James M.: Pneumococcic Endocarditis. Arch. Int. Med. 62: 388, 1938.

Acute endocarditis occurring in the course of pneumococcemia is probably always caused by the pneumococcus.

Acute endocarditis is a considerably more frequent complication of pneumococcic sepsis than is generally believed.

Pneumococcic endocarditis may be diagnosed ante mortem in about 50 per cent of the cases if certain laboratory facilities are available.

Pneumococcic endocarditis usually occurs as a complication or sequel of pneumococcic pneumonia, runs an acute course, attacks especially the valves of the left side of the heart, is characterized by embolic phenomena, and terminates in the majority of instances in purulent meningitis.

As serum and drug therapy of pneumococcic endocarditis has been almost uniformly unsuccessful, therapeusis should be largely prophylactic, namely, the prevention of bacteremia by means of potent specific serum and the removal or drainage of purulent foci.

AUTHOR.

Stewart, Harold J., Heuer, George J., Deitrick, John E., Crane, Norman F., Watson, Robert F., and Wheeler, Charles H.: Measurements of the Circulation in Constrictive Pericarditis Before and After Operation. J. Clin. Investigation 17: 581, 1938.

In the last two and one-half years the authors have observed nine patients suffering from chronic constrictive pericarditis, and in six of these part of the pericardium has been resected. Studies of the circulation have been made before, as well as after, partial pericardiectomy. This paper records the studies of the circulation together with a statement of their experience with surgical treatment.

Chronic constrictive pericarditis is usually associated with decrease in cardiac output per minute and per beat and decrease in the cardiac index. The venous pressure is elevated and the circulation time prolonged, and there is increase in size and caliber of the peripheral venous channels. Rest in bed and medical therapy may occasion clinical improvement with disappearance of the accumulations of fluid and with changes of the circulation toward normal. After operation in those cured, the measurements assumed normal limits, and in those "improved," the measurements of the circulation approached normal. In this syndrome the symptoms and signs appear to be a consequence of the defects in circulation which the constricting pericardium occasions. These defects appear to be two: (1) obstruction to entrance of blood into the chambers of the heart and (2) interference with contraction and emptying of the heart. These result in (1) decrease in cardiac output per minute and per beat and (2) piling up of blood on the venous side, which accounts for rise in venous pressure and slowing of the velocity of blood flow. Releasing the heart and removing obstruction by resection of part of the pericardium results in return of these functions toward or to normal levels.

AUTHOR.

Krumbhaar, E. B., Ehrich, William E.: Varieties of Single Coronary Artery in Man, Occurring as Isolated Cardiac Anomalies. Am. J. M. Sc. 196: 407, 1938.

Two cases of absence of a coronary artery are reported, both incidental findings at autopsy and apparently causing no damage to the myocardium.

In the first case a large left coronary artery continued around the A-V groove to the anterior surface of the right ventricle, giving off branches that corresponded to those normally given off by both arteries (Hyrtl type of absent coronary).

In the second case, a large right coronary artery supplied most of the heart with conventional branches. Near its origin, however, it gave off one large anomalous branch which passed behind the aorta to supply a good part of the left ventricle, and there was another to the ventricular septum. The possibility must be considered that the former of these represents a true left coronary arising from a misplaced anlage, though the similar cases of Bochkalek and Sanes make this very unlikely.

Other cases of absence of a coronary artery, or possibly misplaced anlage or origin, are tabulated, all but three of which fall into groups corresponding to the types of the two cases reported here.

AUTHOR.

Allan, Warde B., and Baylor, John W.: The Influence of Tonsillectomy Upon the Course of Rheumatic Fever and Rheumatic Heart Disease. A Study of 108 Cases. Bull. Johns Hopkins Hosp. 63: 111, 1938.

One hundred and eight patients subjected to tonsillectomy and adenoidectomy because of rheumatic fever, between 1910 and 1924, were reinvestigated in 1935.

Following operation, recrudescences of acute rheumatic manifestations occurred in 43.5 per cent of the patients.

Recrudescences were common in the first five years after operation. Most of the patients who had repeated recrudescences during this period died of rheumatic heart disease.

Patients living for more than five years after operation had almost as many recrudescences after, as during, the five-year period.

Evidence of continued nasopharyngeal infection was prominent in the patients having recrudescences.

Chorea alone was less often followed by severe rheumatic heart disease than was polyarthritis alone.

Rheumatic heart disease occurred more frequently in those having recrudescences, and deaths from rheumatic heart disease occurred only in this group of patients.

The total incidence of rheumatic heart disease was relatively but perhaps not significantly low.

Since rheumatic heart disease developed in only six of the forty-nine rheumatic patients not having cardiac involvement at the time of operation, it is concluded that tonsillectomy and adenoidectomy are to be recommended in the treatment of rheumatic fever.

AUTHOR.

Stroud, Wm. D., and Shumway, Norman P.: Intermittent Claudication as an Early Symptom of Cardiovascular Disease. Pennsylvania M. J. 41: 894, 1938.

Physicians in various parts of the world are considering the possible relationship of intermittent claudication and cramps in the calves of the legs at night with angina pectoris, coronary occlusion, and essential hypertension.

Studies of patients in the heart clinic of a general hospital and those referred for private cardiovascular consultation during the past ten months suggest: (a) There is some relationship between intermittent claudication and coronary occlusion, since there was an incidence in 57 such cases of 7 (12.2 per cent) with intermittent claudication and only one in a control series of 106 patients without heart disease. (b) There seems to be no definite relationship between hypertension or angina pectoris and patients with intermittent claudication. (c) Patients with angina pectoris or coronary occlusion appear to have no more cramps in the calves of the legs at night or in the muscles of the feet or toes than patients with no heart disease. (d) Patients with hypertension are more likely to have such vascular phenomena in the legs while at rest than are patients with no heart disease.

MONTGOMERY.

Hammer, H. J., and Schulte, T. L.: Changes in Blood Pressure Produced by Prostatic Massage. J. A. M. A. 111: 308, 1938.

Prostatic massage causes a rise in systolic and diastolic pressures in most patients. In about 1 per cent of patients syncope occurs, characterized by vasomotor collapse. This occurred in patients whose average age was 39 years.

The vasomotor response to prostatic massage in the series of 378 patients tested showed no relationship to prostatitis, hypersensitivity to the procedure, hemorrhoids or anal fissures, and various nervous states. The rise in blood pressure following prostatic massage was greatest when the patient was in the lying position. Responses of lesser degree were observed among patients in the bent-over and sitting positions respectively.

A comparison of the response of blood pressure following prostatic massage with the rise from the cold pressor test revealed parallel results among both the patients who had normal blood pressure and those who had essential hypertension.

One should bear in mind the possibility of a considerable rise in blood pressure which occurs with prostatic massage in patients with essential hypertension.

NAIDE.

Fatherree, Thomas J., and Allen, Edgar V.: The Influence of Epinephrine on the Digital Arterioles of Man: A Study of the Vasoconstrictor Effects. J. Clin. Investigation 17: 109, 1938.

The demonstration of the vasoconstrictor effect of epinephrine on the digital arterioles requires sufficient vasodilatation which may be obtained satisfactorily in the upper extremities (and at times in the lower extremities also) by placing a heat tent over the trunk. This procedure does not impair the vasoconstrictor effect of epinephrine. However, even under these circumstances the injection of epinephrine into the veins of patients with normally innervated extremities may not cause significant vasoconstriction.

For comparative purposes, the temperatures of the skin of the digits of an individual and the temperature of the environmental air must be approximately the same on the different occasions of a study of the effect of injecting epinephrine. Even under these circumstances the results are very variable.

In normally innervated extremities, epinephrine ordinarily produces a slower but more prolonged vasoconstrictor effect in the toes than in the fingers, but there is no constant difference in the magnitude of vasoconstriction, induced by the injection of epinephrine, in the fingers as contrasted with that in the toes.

In subjects with normally innervated extremities, the vasoconstrictor effect of epinephrine on digital arterioles varies widely. Marked variability in the response of the skin temperature of different digits of the same individual and in the response of the skin temperature of the same digit of the same individual on different occasions has been noted. There is some doubt that the response of the temperature of the skin of the digits to the intravenous injection of epinephrine is as reliable a test as has been previously reported.

Patients with vasomotor symptoms suggesting Raynaud's disease do not necessarily possess arterioles which are unduly sensitive to epinephrine. Conversely, great sensitivity of digital arterioles to epinephrine does not necessarily indicate that vasomotor symptoms occur clinically. These observations cast some doubt on the conclusion that the recurrence of vasomotor symptoms after ganglionectomy for Raynaud's disease is due to an increased sensitivity of the arterioles to epinephrine.

AUTHORS.

Davis, Perk Lee: Congenital Absence of the Superficial Volar Arch: An Arteriographic Study. Radiology 31: 137, 1938.

A case of vasospasm is reported with congenital absence of the superficial volar arch as proved by arteriography.

AUTHOR.

Sandstead, H. R., and Beams, A. J.: Relief of Diabetic Pain of Neurocirculatory Origin by Oral Administration of Sodium Chloride. Arch. Int. Med. 61: 371, 1938.

Observations were made on thirteen diabetic patients, ten with pain of neuritic origin and three with pain of arteriosclerotic origin. From 11 to 60 gm. of sodium chloride were given for from twenty days to six months. The pain was relieved, and the circulation in most instances was improved.

MONTGOMERY.

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Original Communications

THE DYNAMICS OF HYPERTENSION*

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HYPERTENSION, like other diseases, represents an experiment which nature performs on human beings. Physicians are concerned, not merely with the problem of establishing the existence of hypertension, but also with that of interpreting the kind of experiment going on, to the end that the human experiment may be terminated or that the natural compensatory mechanisms may be aided. Physicians have been helped in these tasks by applying information gained through an orderly solution of fundamental problems regardless of their practical importance. They have likewise been assisted through use of apparatus designed and tested in laboratories. But this has proved inadequate, hence the efforts to hasten our understanding of the hypertension problem by more pertinent types of animal experimentation. Now, observations and data gained from such experiments, and also from patients, again raise problems which need to be referred to laboratories of fundamental science for reinterpretation or additional study.

Our greatest and perhaps only hope of elucidating and alleviating human hypertension rests on such shuttling of problems between the clinics and laboratories of basic experimental sciences. Those who are attempting to curb or prevent animal experimentation in any of these fields by law should reflect on the impossibility of abrogating nature's hypertension experiments by similar legislative action.

EXPERIMENTAL AND CLINICAL HYPERTENSION

Persistent experimental hypertension can be produced, among other ways, (1) by midbrain lesions, e.g., by intracisternal injection of kaolin,

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(2) by section of all known moderator nerves, or (3) by damage to the kidneys, through ligation of ureters, by permanent constriction of the renal vessels, etc.

The last-named procedure, which we owe to Goldblatt and his associates,[1, 2, 3] is the most certain method yet devised for producing a persistent form of hypertension. Section of all the moderator nerves likewise causes a prolonged hypertension. But certainly it is not permanent unless all of the moderator nerves are cut, and even under these conditions it apparently fails occasionally.[4, 5] This suggests either that very few filaments suffice to stabilize blood pressure or, more probably, that direct cardiovascular compensations are adequate to re-establish normal pressure levels. In contrast to the hypertension induced by renal ischemia, which is not prevented or abolished by denervation of the kidney, by section of the splanchnic nerves, excision of the lower four thoracic ganglia, section of the sixth dorsal to second lumbar anterior roots, total sympathectomy, or destruction of the spinal cord, this form is prevented or abrogated by total sympathectomy or removal of all thoracic and sympathetic ganglia, but not by splanchnectomy alone (for review see Goldblatt[1]). In short, it appears probable that either nervous or unknown humoral factors can be concerned in prolonged experimental hypertension.[6, 7, 8, 9, 10]

A candid evaluation of the reported evidence inclines one to the belief that essential and renal hypertension in man are likewise basically due to unknown humoral agents, but that, as in transient hypertension of normal individuals, vasoconstriction of nervous origin may be superimposed periodically or permanently. This squares with various observations: Significant reduction of pressure occurs in many patients as a result of mental and physical rest; blood pressure may be reduced abruptly, but not quite to normal levels, upon compression of the carotid sinus.[11, 12, 9] The peripheral vessels are still capable of dilating in response to heat.[13] The idea of a dual mechanism is also supported by the surgical demonstration that section of efferent vasomotor fibers in the anterior spinal roots or of the splanchnic nerve seems to be beneficial, but may not permanently reduce pressure to normal levels.[14, 15, 16] The evidence that the disturbed nervous mechanism is due to failure of moderator nerves, rather than to disturbance of central origin, does not appear to have much experimental or clinical support. The frequent association of essential hypertension with continued nervous tension, emotional stress and anxiety, as well as the proximity of emotional and hypothalamic vasomotor centers, favors a central origin. It is a priori improbable that nature could easily abrogate all afferent moderator influences, which seems to be necessary to evoke hypertension in animals.

Dynamic Resemblances and Differences.—The zealous search for the humoral and nervous factors concerned in experimental hypertension has temporarily eclipsed careful study of the dynamic changes produced.

so that we can only say that these seem to resemble those of human hypertension. It has been pointed out that experimental hypertension due to severance of moderator nerves is usually accompanied by tachycardia, which is the exception rather than the rule, clinically.[17, 12, 18] That increased cardiac output contributes to elevation of pressure in such instances seems probable. In patients, however, the heart rate and output are generally within normal ranges or even less,[19, 18] and therefore do not appear to be significant factors in the production of hypertension. Such tachycardia is apparently not conspicuous in experimental hypertension of renal origin, although heart rates during the course of developing hypertensions have neither been reported nor analyzed with the detail that dynamic studies merit. Cardiac output and viscosity studies are also not often made in experimental investigations. Indeed, the chief fact established seems to be that systolic and mean pressures are elevated appreciably. Fewer observations on diastolic pressure[20, 21, 22] indicate that it increases rather variably but on the whole less than systolic. The pulse pressure also increases from 30 to 35 per cent. This is much less than is frequently found in patients, in whom increases of 200 per cent or over are not uncommon.[23] To what extent this is caused by the faster heart rates in dogs remains to be determined.

Blood Pressure Measurements in Animals.—It must be admitted frankly that blood pressure readings on animals cannot be accepted with the same degree of surety as in man. This is partly due to the difficulty of utilizing indirect blood pressure recording apparatus on animals and partly to the dilemma of determining when dogs are under basal conditions.

The form and size of the animal's limbs are not designed for application of blood pressure cuffs and despite earnest efforts to overcome these obstacles the author is not convinced on the basis of personal experience that consistent errors are not incurred. Aside from this, pressures in the femoral arteries generally exceed those in the aorta[24, 25, 26] and are more likely to vary independently of aortic pressure[27] than are pressures in the carotid artery. Since we desire evidence regarding pressure variations in the aorta, alterations in femoral pressure cannot be trusted to yield this information. Our best approach is through the use of van Leersum loops of the carotid artery.

With the achievement of direct registration of arterial pressures by the calibrated hypodermic manometers introduced by Hamilton[28, 29, 30] and modified by Gregg,[31] more accurate determinations are possible. At least one such report has been made.[21] However, use of such apparatus involves special training in order to avoid the many pitfalls which beset all optical pressure recording. Hence it can only be recommended to those who are qualified by training and experience in the use of such instruments as well as in the evaluation of the records obtained.

Equipped with such technique, the experimenter is still hampered by the fact that even in so-called "trained" dogs, the blood pressure is much more labile than in human beings. The mere puncture of an artery under local anesthesia or application of pressure cuffs may be sufficient to modify heart rate and blood pressure temporarily. Since the properly trained dog under basal conditions exhibits a considerable degree of sinus arrhythmia, I hereby propose as a criterion of the basal state the existence of some degree of arrhythmia. Its absence in normal dogs probably indicates that they are not sufficiently at ease.

The patient experimenter, however, is merely pushed from one cul-de-sac to another, for the presence of such arrhythmia causes systolic and diastolic pressures to fluctuate from beat to beat. This is indicated to a mild extent in the record of Fig. 1, for which I am indebted to my colleague, Dr. Gregg. The experimenter must therefore choose between reporting the highest and lowest readings for systolic and diastolic pressures or the averages from a complete cycle of arrhythmic beats.

The foregoing considerations indicate some of the difficulties that confront experimenters in determining with exactness the degree of hyper-

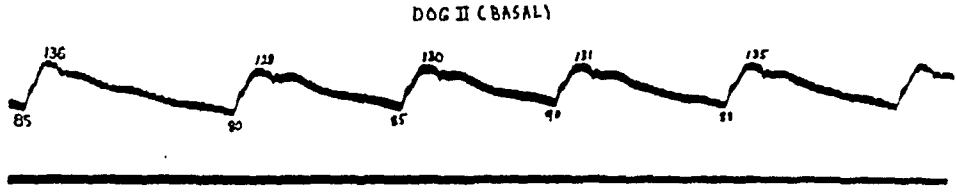

Fig. 1.—Pressure variations in carotid artery of normal unanesthetized dog under basal conditions.

tension induced by various procedures. It has added materially to the difficulty of analyzing and comparing the dynamic states in animals with those in man and, as a matter of fact, in differentiating ubiquitous accidental fluctuations from those actually produced by a causative agent. In the interest of further progress we must recognize the unconquered difficulties, as well as applaud the achievements despite their existence.

THE INCREASE IN PERIPHERAL RESISTANCE

Many types of observation indicate that in renal as well as essential hypertension, blood volume, blood viscosity[32, 33, 12] and cardiac output[19, 18] fall within normal ranges; hence the inference based on Poiseuille's law that increased peripheral resistance must necessarily be the primary factor.

The Concept of Central, Collective, and Effective Resistances.—In order to avoid misinterpretations, we must be clear in regard to various conceptions of "vascular resistance." The ejection of blood from the left ventricle is impeded by a central resistance in the root of the aorta. It represents the load of the left ventricle. It has three components: (1) the frictional resistance to flow through the central vessels and distribut-

ing branches, (2) the resistance offered collectively by all the prearterioles and arterioles which regulate the efflux from the arterial tree into the capillaries, and (3) the resistance offered distal to arterioles by changing size and patency of capillaries or by the head of venous pressure beyond them.

(1) The functional resistance between the blood and the walls of the larger arteries normally constitutes 20 to 25 per cent of the total central resistance and remains fairly constant under various conditions, including greater rigidity of the vessels. As Fahr and his associates[34, 35] point out, the resistance involves (a) static changes due to alterations in lumen (e.g., changes due to age, pathologic processes, or to differences in internal pressure) and (b) dynamic changes which vary with the degree of expansion during each systole. Rough physical calculations indicate, however, that extreme static and dynamic changes such as occur in severe arteriosclerosis probably do not cause more than a 2.5 per cent alteration in the total central resistance.

(2) Changes in the caliber of the arterioles, which act as the stopcocks of the arterial tree, constitute the dominant factor affecting the total central resistance. The arteriolar resistance is not the same in all regions of the body; for example, it is high in the leg as compared to the head. Furthermore, these relations may vary greatly during nervous or chemical actions.

The net resistance offered by all the arterioles collectively is generally designated as the peripheral resistance, or better, the effective peripheral resistance. It is obvious that increase in the effective peripheral resistance does not necessarily imply greater impediment to flow through all arterioles and prearterioles. Constriction of vessels with powerful muscular fibers may elevate pressure so much that arterioles like those of the brain or the limbs, containing fewer contractile elements, may be passively expanded and their local resistance actually decreased. Again, active constriction may occur in one region and active dilatation in another, in which event the change in effective peripheral resistance would be a resultant of two contrary changes. The physiologic principle emerges that it becomes hazardous to draw conclusions regarding changes in the effective peripheral resistance from observations of a single organ or a limb.

(3) Active changes in the size of capillaries and the pressure on the venous side of the capillaries may exert an additional influence on peripheral resistance, e.g., in shock. It is, however, the writer's impression that its dynamic importance was exaggerated during the years of enthusiastic study of capillary actions. Certainly there is little evidence that capillary or venous resistances are important factors affecting the central resistance during hypertension except when venous congestion supervenes during ultimate decompensation.

Such considerations allow us to look upon changes in the effective peripheral resistance as essentially synonymous with alterations in central aortic resistance.

The Magnitude of Increase in Effective Peripheral Resistance and Its Relation to Blood Pressure.—The generalization that the peripheral arterioles are chiefly involved both in renal and essential hypertension is substantiated by the clinical observations that the greatest drop in pressure still occurs in the arterioles of limbs[36, 37] and that the blood flow through the arm or hand is within normal limits despite the higher brachial pressures.[12, 13]

Such samplings of local peripheral resistances of course give no information as to the collective or effective resistance to flow from the

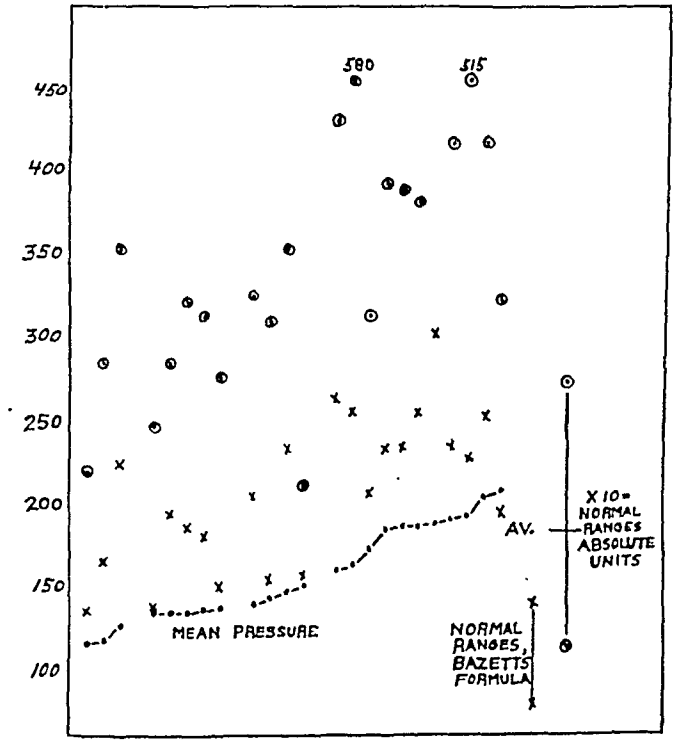

Fig. 2.—Plots showing relation in patients with hypertension of mean pressure (lower curve) to effective resistance calculated in absolute units (⊙) and in Bazett units (×). Ordinate values for absolute units should be ×10.

arterial tree. Fortunately this can also be calculated either in absolute or arbitrary units by use of several formulae,[38, 39, 40] although to my knowledge no effort has previously been made either to demonstrate the existence of an augmented collective resistance in hypertension or to gauge the extent of the increase by such a procedure.

Using the convenient equation, $R = 3\frac{Pm}{Vt/A}$, in which Pm = mean pressure in mm. Hg. and Vt/A = the cardiac index, Bazett, Cotton, et al.,[38] by refined technique, calculated arbitrary values ranging from 79 to 138 for normal subjects. Recalculating their results by using one-half systolic plus diastolic pressure for mean pressure causes no significant

difference. The values range from 80 to 139 arbitrary units. If in a similar manner we calculate R for hypertensives from data published by Soma Weiss and associates,[18] it can readily be seen from Fig. 2 that all of these cases show some augmentation of effective resistance. While, as a rule, it increases with mean pressure, this is by no means invariably true. Some patients with very extreme elevation of pressure have no greater effective peripheral resistance than others with very moderate hypertension. This suggests that augmented peripheral resistance is not the only coefficient in clinical hypertension.

Similar conclusions can be drawn when effective resistance is calculated without regard to surface area, using the formula $R = \frac{Pm \times 1332}{Vt} = \frac{\text{dynes} \cdot \text{sec.}}{\text{cm.}^5}$, in which Vt denotes cardiac output per second. Plots of such values are shown in the upper graphs of Fig. 2, in comparison with the extreme and mean values in normal subjects reported by Böger and Wezler.[39] A more extended use of such calculations in clinical practice might easily lead to a better subdivision of cases than now exists, and its extension to experimental hypertension would offer better comparisons with human forms than do studies of blood pressures alone.

While considering the topic of peripheral resistance and its calculation, we may allude briefly to the question whether concurrent diminution of vascular distensibility so commonly found in hypertension might affect the effective resistance. The possibility exists that the altered form of the pressure wave reaching the peripheral arteries and perhaps the arteriolar orifices could modify the net efflux and hence the calculated peripheral resistance. We have recently studied this question by the aid of circulation models in which a mechanical resistance was kept fixed while the elasticity of the system was quickly diminished. In such experiments, illustrated by data in Fig. 2, calculation of the resistance in absolute units, as above, showed that these figures change very insignificantly as a result of a great increase in rigidity of the artificial aorta, regardless of whether the peripheral resistance was large or small when rigidity was created.

Territorial Distribution of the Augmented Resistance.—Physiologic experiments beginning with the studies of Ludwig and von Cyon[41] and the early studies of Bayliss and Bradford[42] have demonstrated that an intensive constriction of smaller vessels must occur in normal animals in the splanchnic area in order to cause an elevation of pressure equal to that found in hypertension.

The following facts seem to have been demonstrated: (1) Excitation of nerves to a limb or of the nerve roots between the second thoracic and fourth lumbar causes no rise of mean pressure in animals, provided the splanchnic nerves are cut during stimulation of the lower nerves. (2) Stimulation of the splanchnic nerves produces a great elevation of pressure even after removal of the adrenal glands. (3) In atropinized animals, under mild artificial respiration, similar in-

creases in blood pressure accompanied by decrease in the volume of abdominal organs and increase in that of the limbs can be produced by excitation of pressor fibers in the sciatic and vagus nerves. These effects are greatly reduced or absent after section of the splanchnic nerves. (5) Ligation of the main branches of the aortic arch, together with the common iliacs, does not significantly alter the calculated effective resistance (our observations). (6) Compression of the aorta progressively upward as a rule causes no pressure elevation until a clamp is applied above the origin of the superior mesenteric vessels.

These and other experiments lead to the reasonable inference that if arteriolar constriction is the primary and chief cause of human and experimental hypertension, the splanchnic area must be dominantly involved. This does not preclude simultaneous constriction of vessels in other organs or in the limbs, for which evidence has apparently been produced, among others by Pickering[12] and by Prinzmetal and Wilson.[13] But any thesis that their contraction can add significantly to elevation of general blood pressure lacks proof. It is conceivable that the greater relative mass of human limbs might make a difference. But nowhere in the literature have I found evidence that dilatation of arm vessels following nerve anesthesia or application of heat reduces hypertension significantly. On the contrary, it is well known that complete deprivation of the circulation to limbs in organic or spastic types of vascular disease, or total loss of several limbs, does not cause even a moderate hypertension.

The Nature of the Arteriolar Resistance.—Successive observation by Gull and Sutton (1872), Jores (1904), Evans (1920), Fahr (1922), and others that thickening of the walls of minute vessels occurs led to the view that generalized changes in the intima and media of smaller vessels are responsible for the augmented peripheral resistance. However, attention has been directed repeatedly to the fact that the lesions are more often limited to a few organs, the kidney, spleen, pancreas, liver, brain, and retina being involved in order of frequency and severity. With the detection of similar arteriolar changes in biopsies of skeletal muscle[43, 44] it seemed probable for a time that organic changes might be more general than was then believed. Subsequent studies[45, 46] seem to have shown that such preparations do not necessarily give information regarding changes in vessels of the internal organs. Furthermore, it is debatable whether the lumina are actually decreased during life.

Lacking a sound morphologic basis for an augmented resistance the view naturally shifted to the postulate that a sustained functional contraction, unwisely designated vascular spasm, results through the action of humoral or nervous agents. No one, however, has submitted good visual or photographic proof of the occurrence of such constriction except in the retinal vessels. Microscopic studies of blood vessels in the skin and nail bed, originally undertaken by Lombard,[47] have not proved as helpful as was hoped. Our evidence is entirely indirect, i.e., based on the calculation of effective resistance.

THE ROLE OF LARGER ARTERIES IN HYPERTENSION

Physical Importance of Arterial Elasticity.—By virtue of their large caliber and highly elastic walls, the aorta and its immediate branches act like the compression chamber (Windkessel) of a fire engine in that they buffer variations in pressure and flow.[48] Experiments on circulation models indicate that when peripheral resistance and output remain the same, an extreme increase in rigidity of larger vessels acts chiefly to redistribute systolic and diastolic efflux from the system, thereby increasing systolic, and decreasing diastolic pressure. Mean pressure either remains unchanged or may rise or fall a trifle (Fig. 3). Fahr, Davis, and Spittler[34, 35] found similar changes when the naturally beating heart constitutes the pump. The conclusion seems to be clear that a rise of both pressures with significant increase in the mean pressure, such as occurs in hypertension, can occur only when peripheral resistance is augmented in

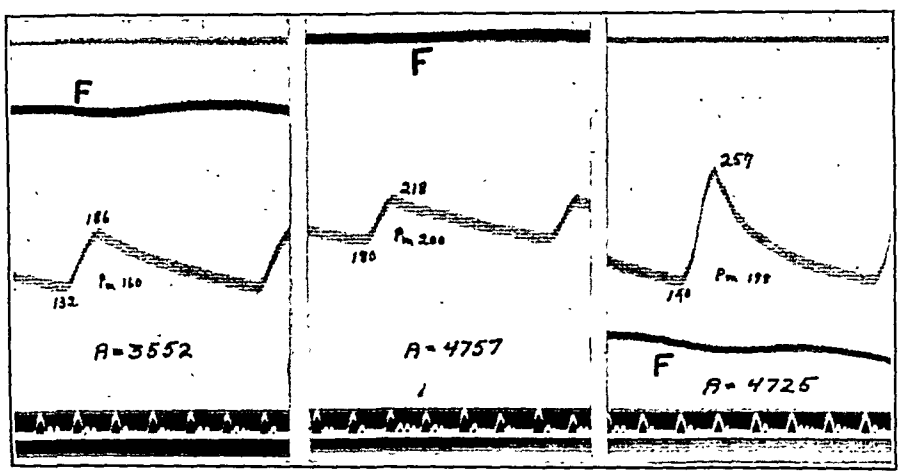

Fig. 3.—Three pressure pulses recorded optically from circulation model. *A*, *B*, Effect of increasing peripheral resistance on pulse pressure and calculated effective resistance. *C*, Effects on pulse pressure, mean pressure, and calculated effective resistance of superimposing rigidity of central vessels, while actual peripheral resistance remains the same in *B*. Records *F* indicate peripheral volume flow. Compensated in *B*. Note reduction in *C* as result of arteriosclerosis and fall of mean pressure.

addition. This does not signify, however, that provided peripheral resistance is increased, diminished elasticity of the central vessels may not accentuate the height to which systolic pressure is elevated by the force of the ventricular contractions. This is clearly shown by comparing curves A, B, and C of Fig. 3. An increase in effective resistance from 3,552 to 4,757 absolute units decreased the pulse pressure and increased the mean pressure from 160 to 200 mm. Hg. With essentially the same peripheral resistance of 4,725 absolute units, superposition of a less elastic state of arteries increased systolic and reduced diastolic pressures.

It has often been suspected that diminished extensibility of the central vessels in this way contributes to the elevation of systolic pressure in many cases of hypertension. Furthermore, a grave suspicion exists that

this means not merely a normal decrease in expansion of vessels such as occurs at higher internal pressure, but rather that some functional, physical, or structural alteration, perhaps in the nature of premature aging, is concerned. However, it has proved difficult to obtain good tangible proof for its existence.

The Effects of Age on the Structure and Physical Characteristics of the Aorta.—Although arteriosclerotic changes exist in the aorta and palpable vessels in some individuals with hypertension, it is generally conceded that severe hypertension occurs without its presence. In addition, and quite apart from such obvious pathologic changes, it is well known that the aorta of normal individuals undergoes certain changes with age. The lumen begins to increase at puberty and by the age of forty years may be even greater than the sum of the cross sections of its branches.[38, 49] Coincidentally, the walls gradually become thicker, their elastic tissue decreases, the collagenous fibers seem to increase, and their distensibility with increasing pressures is reduced according to well established rules.[50-54] The trend is indicated by the curves of Fig. 6, which will be discussed later.

Since the volume-elasticity coefficient, $\frac{dp}{dv}V$, which expresses the degree of rigidity, depends on the ratio of pressure to volume increase, $\frac{dp}{dv}$, as well as on the diastolic volume, V, changes in size and distensibility tend to neutralize each other during the process of normal aging, as far as the central "compression chamber" function is concerned. If, however, changes in size and elasticity are not thus adjusted, the buffering function of the central reservoir suffers. But studies of human vessels by microscopic or physical methods are not numerous enough to warrant deductions as to the existence of such maladjustments of distensibility with respect to size during hypertension in different age groups, and even if such relations were established with meticulous care on autopsy material the suspicion would still remain that the observations might not apply to the vessels during life.

The possibilities also exist that physical changes in elasticity may precede evident histologic alterations, or that functional variations in elasticity may occur during life as a result of altered muscular action. Hochrein and Lauterbach[55] presented a few cases which seem to support the first of these possibilities.

The Role of Muscular Action.—How muscular contraction affects the volume-elasticity coefficient in the aorta and its branches remains debatable. In distributing arteries, contraction of circularly disposed, spindle-shaped muscle fibers reduces the size (V) and increases the ratio, $\frac{dp}{dv}$, particularly at lower ranges of pressure. The effects in the aorta and its immediate branches are debatable. Indeed, the arrangement and purpose of the muscular elements remains an enigma. The

muscle cells are sparse and no longer spindle-shaped. They assume broad, short, irregular forms; sometimes they are serrated, stellate cells, the branches of which perhaps fuse, forming a syncitium.[56] I have always doubted whether such cells can have any significant influence on vessel size or elasticity. Hürthle[57] presented results which he interprets as indicating that the aorta participates actively in forcing blood into the iliac branches. Bazett, Scott, et al.,[38] on the basis of pulse velocity studies, believe that their contraction decreases the elasticity of the aorta significantly. According to Benninghoff,[56] the muscle fibers are arranged radially or tangentially and are so joined to wavy elastic fibers that in contracting they straighten these elements and reduce their tension. If this is true, muscular contraction should increase the lumen slightly and the elasticity significantly.

We may hasten to add that experimental evidence of a routine sort does not seem to support this pretty theory. Rings of large arteries, as well as of smaller muscular vessels, have repeatedly been placed in oxygenated Locke's solution and their reactions tested. Under proper conditions they respond by decrease in diameter upon direct mechanical, electrical, chemical or thermal stimulation.[58, 59] The subject, however, deserves further experimental study of a more direct sort.

Pulse Velocity Studies as Criteria of Elasticity Changes.—Since the velocity of pulse wave transmission is related to the square root of vascular distensibility, as expressed by the formulae of Moens,[60] O. Frank,[61] Bramwell and Hill,[62] and others, the uninitiated are likely to assume that abnormal states of elasticity in patients with hypertension should be easily detectable by this means. Time is lacking to deal adequately with the numerous complications and hazards that attend use of the method. Laborious researches have shown that the pulse velocity is less in central than in peripheral vessels, that it increases with age, that it depends on the pressure within the vessels, and, in peripheral distributing vessels, at least, also on the state of muscular contraction. But still no uniformity of opinion exists as to whether the propagation rate in any set of vessels is faster in cases of hypertension when correlated with pulse velocities of normal subjects of similar ages, similar pressures, etc.[63]

In 1932 I reviewed[23] the advantages and also some of the errors that may enter into an ingenious method proposed by Bramwell and Hill,[62] viz., that of exerting variable counter pressures by means of a blood pressure cuff and measuring pulse velocities at different *effective internal pressures.* Those who have used this procedure[63] have been unable to establish significant differences between patients and normal subjects.

Attention may now be directed briefly to the recent proposal by German investigators[39, 55, 64] to establish quotients of $\frac{\text{peripheral velocity}}{\text{central velocity}}$, a procedure which has the merit of evaluating changes in different vessels at the same time, in the same person. However, variations with age and blood pressure still need to be established through correlation studies. A

limited number of normal quotients at different ages, together with those from eleven cases of hypertension analyzed by Böger and Wezler,[39] are incorporated in the lower graph of Fig. 4. From such data, which appear altogether too few in number, and from changes which are too small, they conclude that the quotient increases in young individuals with hypertension but decreases in older persons with hypertension. This and other studies lead them to support Benninghoff's conception that muscular contraction increases the distensibility of larger vessels and that abrogation of such contraction decreases their distensibility in hypertension. I have similarly calculated and plotted quotients from the much larger number of normal subjects and patients with hypertension recently studied by Haynes, Ellis, and Weiss.[63] As indicated by the upper

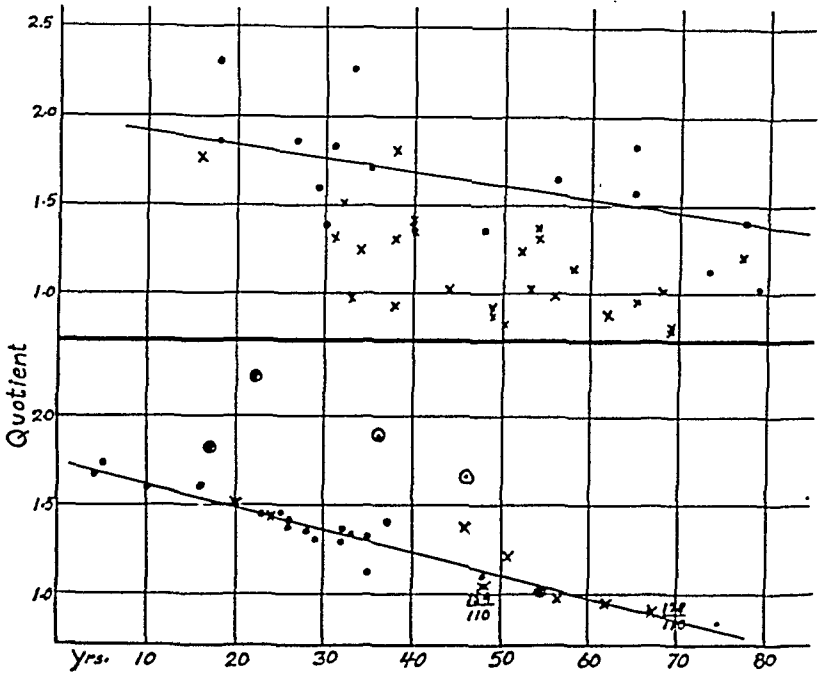

Fig. 4.—Two sets of plots showing quotients, $\frac{\text{central pulse velocity}}{\text{peripheral pulse velocity}}$, in normal subjects (dots), and in subjects with hypertension (× and ⊙). Upper series from data of Haynes, Ellis, and Weiss. Lower series from data of Böger, Wezler, and Hochrein. Note general tendency of normal quotient to decrease with age. Ordinates = quotients; abscissae = age. Discussion in text.

plot of Fig. 4, the quotients of patients with hypertension at all ages seem to be lower than normal. If any conclusion is permissible, it would be that the elasticity of central vessels is reduced rather more than that of the limb vessels.

It is hazardous, however, to place too great confidence in these, or in other types of pulse velocity study, for while significant improvements have been made in the technical methods for recording pulses, the problem of accurate measurement of actual arterial lengths has not been conquered. If we take cognizance of the diversified architecture of the arterial tree in different subjects[65] and the variations in vessel lengths due to posture, tortuosity, etc., it becomes apparent that the small differ-

ences in velocity occasioned by considerable changes in elasticity may be obscured or apparently exaggerated through imperfect measurement of distances.

The Augmented Pulse Pressure and Altered Pressure Pulse in Clinical Hypertension.—The term *pulse pressure*[66] refers to the difference between systolic and diastolic pressure. As determined by clinical methods this gives an index of the extreme variations of pressure. The term *pressure pulse*[67] was introduced to incorporate all the pressure variations occurring from moment to moment during the cardiac cycle. It is the pressure curve recorded by calibrated optical manometers inserted into arteries. A subclavian pulse recorded in man by use of optical methods gives the form of these pressure variations without ordinate values. The

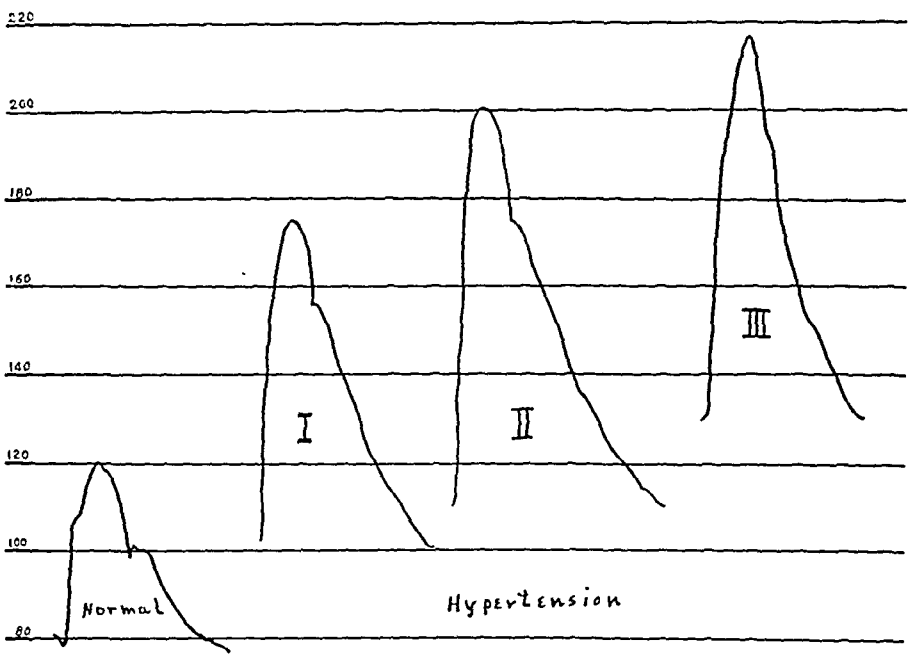

Fig. 5.—Four transcribed pressure pulse curves reduced to the same ordinate values by use of Green's coordirectograph. First curve from normal medical student, for comparison. I, From patient with essential hypertension, aged 37 years; II, from patient with nephrosclerosis (aged 59 years); III, from patient with general arteriosclerosis (aged 61 years).

latter can be supplied, with not too great an error to be useful, if the readings of systolic and diastolic brachial pressures are used as values for the highest and lowest points of such a curve and equal divisions are made between these ordinates. When this is done in the case of hypertension and records are redrawn with equal ordinates, curves such as are reproduced in Fig. 5 are obtained. The first is from a normal medical student, the other three from cases of hypertension recently studied at the University Hospitals.

In 1932[23] I concluded that the form of such pressure pulses and the enormous increase in their amplitude over the normal could only be explained by assuming that the elasticity of the larger vessels is decreased. The evidence upon which this conclusion was based may briefly be re-

stated: (1) Pulse pressures declined with increasing resistance—up to pressures of 200 mm. Hg—when an isolated dog's aorta was perfused with rhythmic variations of pressure, whereas it increased after the aorta had been gradually hardened by formalin. (2) The form of the pressure pulse obtained in hypertension (Fig. 5), with its abrupt rise, peaked summit, and rapid decline, resembled that from an aorta hardened by formalin perfusion. (3) The clinical evidence, which has been since supported by data obtained by better methods, suggests that increased systolic discharge is not a probable factor.[18, 19]

Soma Weiss and his co-workers,[18] who have diligently studied patients with hypertension for many years, were recently forced to the same conclusion, despite their failure to find changes in velocity that deviated from the normal. Volhard[68] has long insisted that it is the larger vessels which are predominantly involved in so-called "red hypertension." Two facts have compelled me to reconsider these opinions: (1) A number of friends whose opinion I respect have suggested that at pressures variously placed between 80 and 140 mm. Hg the distensibility even of youthful arteries may diminish so much that larger pulse pressures may be expected with increasing peripheral resistance. If this be the case one need not assume an additional decrease in rigidity to explain the large pulse pressures in hypertension. (2) I have reported[23] that reflex vasoconstriction in the dog does not decrease pulse pressure, but uniformly increases it.

(a) Circulation Model Experiments.—Changes in elasticity resembling those found in man as a result of aging or pathologic processes[50-54] cannot be reproduced easily in animals, and if reproducible would certainly introduce conflicting reactions in cardiac rate and output. Therefore physical tests were again made on circulation models. In these, cardiac rate and output can be kept constant and the interacting effects of changes in peripheral resistance and distensibility can be studied. The results, reported in detail elsewhere,[69] can be quickly surveyed by the aid of a single graph (Fig. 6). The curved lines represent a selected series of volume-pressure relations at different pressure levels which could easily be reproduced in the machine and were determined each time. Curve *A* is that of an ideally expanding system in which the relations $\frac{dp}{dv}$ are linear. Curve *B* likewise shows a linear proportionality up to 100 or 120 mm. Hg, but beyond this distensibility decreases progressively. Such a curve is fairly comparable to that obtained in young adults. Curve *C* shows a diminution of distensibility at pressures around 60 to 80 mm. Hg; and approximate curves obtained from human aortas during middle adult life, curve *D*, show great reduction of distensibility at very low pressures and a total expansion that is never very great. Curves C^1 and D^1 illustrate the changes when the distensibility is the

same as in *C* and *D*, but the capacities of the system at 20 mm. Hg internal pressure were 35 and 70 per cent larger with respect to the systolic discharge.

The effects of increasing the peripheral resistance on pulse pressure under these different conditions were recorded by a calibrated optical manometer, but for convenience they are directly superimposed on the volume-elasticity curves. For original curves see Wiggers.[69]

In a system in which the volume-elasticity curve is a straight line (curve *A*), pulse pressure decreases to the very limit of the system (beats 1 to 5). When the distensibility begins a progressive decrease at about 120 mm. Hg, as in curve *B*, the pulse pressure decreases uniformly except

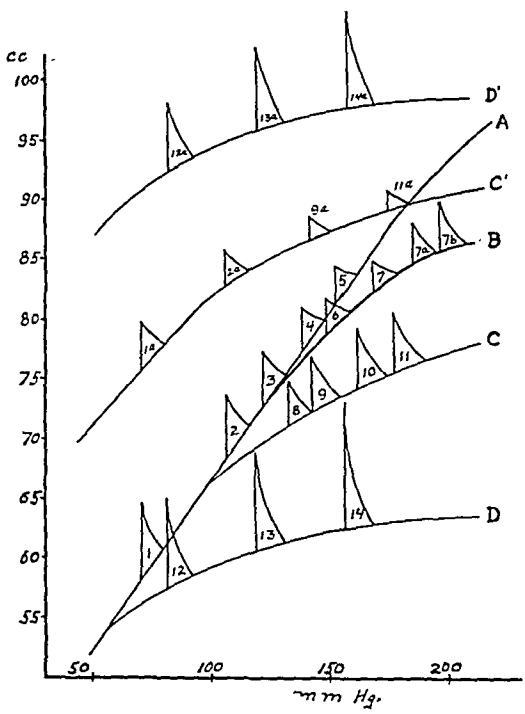

Fig. 6.—Series of graphs illustrating volume-elasticity coefficients at different pressures (abscissae) and the essential changes in pulse pressure found in a circulation model under these conditions. Discussion in text.

at the very uppermost ranges, where it may become larger again (beats 7a, 7b), but never exceeds that of beats at lower pressures (e.g., beats 1, 2).

If, as in curve *C*, the distensibility begins to diminish at about 85 mm. Hg and thereafter decreases rather more, the pulse pressure is still reduced until the pressure reaches about 120 mm. At higher pressures it increases rapidly, but at very high pressures, the beats (10 and 11) are not generally larger than beat 1, though they are larger than beats 2 or 3. This effect is annulled by a 35 per cent increase in the initial volume, as shown in curve C^1. If, as post-mortem studies indicate, the size of the aorta also increases with age, only a reduction in pulse pressure could be anticipated in individuals during middle adult life. If, finally, expan-

sion of the arterial system is limited from the start and the extensibility curve shades off at lower levels, as in old age (curve *D*), the pulse pressure increases from the start and becomes progressively larger. The magnitude of the increase is reduced by a 70 per cent increase in vascular volume (curve D^1). This is shown by comparison of beats 12, 13, and 14 with 12a, 13a, and 14a.

If the facts thus established are applicable to man, they suggest (1) that the importance of diminishing elasticity with increasing pressure as a factor which determines directional changes in pulse pressure has been greatly overestimated, and (2) that granting an unaltered heart rate and systolic discharge, such large pulse pressures as are found in patients with hypertension (Fig. 5) cannot occur except in very old people without assuming an additional rigidity.

(b) Studies on Animals.—I would be among the last to claim that observations on such artificial circulation schemes can be regarded as the final court in deciding the operation of mechanisms in the body. They do, however, allow a first approximation toward guiding principles which can then be further tested on living animals. Fortunately, the changes in pulse pressure observed in persistent experimental and human hypertension can also be produced acutely in animal experiments. This permits the problem to be returned to physiology laboratories for that intimate analysis of dynamic factors which is only possible in acute experiments.

Several types of experiments are in progress which throw further light on the situation in the body. In a first series of experiments the aortas of dogs which had recently died or were in the process of dying were left in situ and perfused with the pump of the circulation model. In this way the effects of increasing peripheral resistance could be tested on the aorta under natural conditions, for the possibility has been suggested[51] that since the aorta in the body is bound down by the adventitia it may be less expansile than tests on removed sections indicate. To obviate ligation of numerous branches, a very thin rubber "inner tube" was passed down the ascending aorta to the iliac branches. To our astonishment, volume-elasticity curves obtained under such conditions in ten street dogs resembled those of *A* in Fig. 6. Diminishing distensibility first became evident at pressures near 200 mm. Hg. It is, therefore, not surprising that a progressive increase in peripheral resistance caused a continuing decrease in pulse pressure. It may be suggested that curves resembling those of *B* and *C* obtained in post-mortem studies of the human aorta may have resulted from post-mortem contraction or even a state of rigor mortis in vessels examined some time after death.

In a second series of experiments, we further studied the possible causes of the increase in pulse pressure that occurs with pronounced vasoconstriction in anesthetized dogs. Repeated tests showed clearly that systolic discharge increases immediately with the rise in blood pressure

and becomes steadily greater. The chief cause seems to be an augmentation of venous return due to constriction of the spleen, but the effects of systolic retention of blood and possible increase in epinephrine output during the height of the pressure increase doubtless contribute. Such experiments indicate that the increasing pulse pressure could be fully explained by the greater systolic output.

Since it is possible, however, that the remarkable degree of elasticity exhibited by the aortas of dogs which were in the process of dying or had just died was due to an immediate loss of tonus and may not represent conditions in the living dog, additional tests were made, in association with Dr. Wegria, to ascertain the relation between diastolic and pulse pressures and the degree of expansion at different pressure levels. The latter was obtained by applying a tiny arteriograph to various portions of the descending thoracic aorta, intact within its supporting sheath and with its natural nerve and blood supply untouched. While the investigations are not completed, the results suggest that as a rule a mechanical increase in resistance caused by compressing the aorta just above the diaphragm produces corresponding changes in pressure variations and wall expansion. However, following elevations of pressure produced by reflex vasoconstriction, adrenalin, and pitressin, the expansion is progressively reduced. It therefore appears probable that changes in the capacity and elasticity coefficients of the aorta do participate in the augmentations of pulse pressure obtained experimentally and perhaps also in experimental and human hypertension.

The Peripheral Flow in Hypertension.—If pressure pulses of patients are given ordinate values as suggested, the curves can be integrated by measuring the surface areas beneath a whole curve, or portions of it, and the mean pressure thus calculated by dividing by the horizontal distance. When this is done, as in Fig. 7, it is found that the mean pressure for the whole cycle (*M*) is elevated and bears a variable relationship to systolic and diastolic pressure. In contrast to normal curves, the bottom of the incisura (I, second curve), marking the moment that the semilunar valves come into apposition, always lies much above the mean pressure level in hypertension, whereas it very nearly coincides with it in normal individuals.

The mean pressures during periods of systole and diastole can be calculated in a similar way and are denoted by rectangles (P_{ms}, P_{md}) in Fig. 7. Such a geometric analysis of calibrated curves clearly shows that mean systolic pressure is increased and mean diastolic pressure is decreased. Since these values represent the average forces which drive blood from the aorta and perhaps its large branches during systole and diastole, it becomes obvious that systolic runoff increases and diastolic efflux decreases.

Recent dynamic studies[69] also indicate that as long as the peripheral distributing arteries remain distensible they serve as a buffer which prevents significant variations of flow through the arterioles and capillaries.

In other words, while the distributing vessels receive more blood during systole and less during diastole, the runoff from the arterioles remains fairly constant throughout the cycle. If, however, the peripheral vessels are also involved, the peripheral buffer chamber is lost and the flow through capillaries becomes intermittent. In this manner a capillary pulse can develop despite the existence of marked arteriolar constriction. The idea that capillary pulsations in hypertension and aortic insufficiency cannot occur except through vasodilatation is an incongruity in the field of cardiodynamics. However, whereas capillary pulsations due to vasodilatation occur on account of a systolic acceleration of flow, those associated with large pulse pressure and increased peripheral resistance are due to a periodic reduction of flow later in diastole, i.e., when arterial pressures sink to low levels.

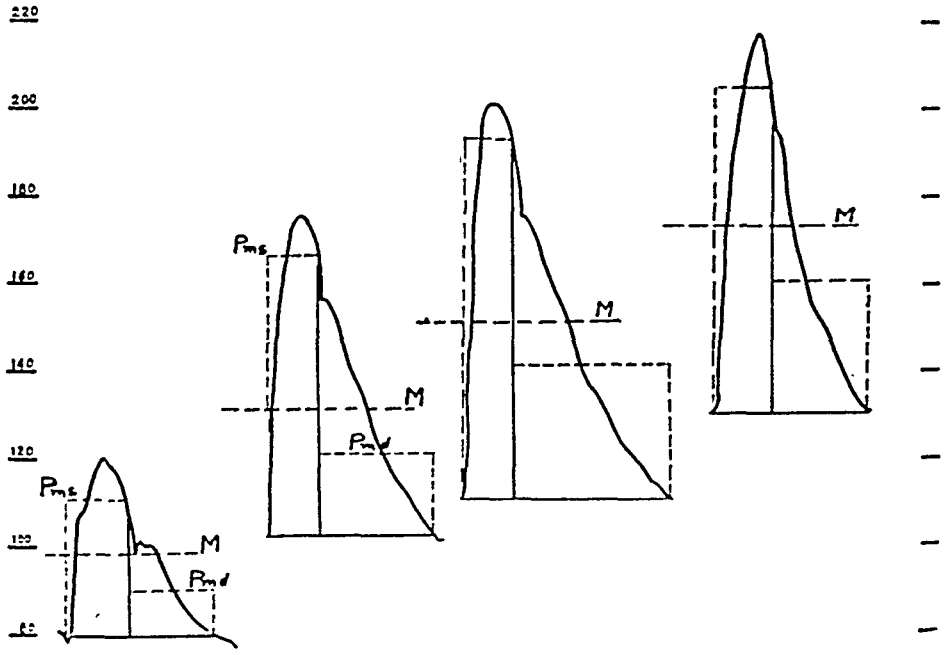

Fig. 7.—Pressure pulses from same patients as those in Fig. 5 showing calculation by integration of values for mean pressure of cycle *(M)* and mean pressures during systole and diastole (indicated by rectangles *Pms and Pmd*). Discussion in text.

CARDIODYNAMICS

The effects of hypertension upon the dynamics of the left ventricle are determined chiefly by the increased load. In acute experiments the systolic output, as determined in various ways, seems to increase somewhat or at least is not diminished as a result of increased peripheral vasoconstriction or aortic compression.[70, 71, 72] By use of a heart-lung preparation and cardiac plethysmograph the mechanism was partially elucidated by Starling, et al.,[70] and by Straub.[73] During the first few beats following a sudden increase in aortic pressure systolic discharge decreases, thereby leaving a small residual volume within the left ventricle. Since normal volumes flow from the left auricle into the left ventricle during

each diastole, the diastolic volume increases, the muscle fibers are stretched, and in consequence the left ventricle contracts more vigorously, thus restoring the stroke volumes to or slightly above normal. We have recently found that translocation of blood from abdominal organs, particularly the spleen, also occurs. This causes an increase in venous return to the heart.

Such a greater systolic output must involve a change either in the velocity or duration of ejection. Starling and his associates emphasized prolongation of ejection. The question was properly raised whether such results are also applicable to the circulation in the body, for the venous pressure is not easily kept constant in heart-lung preparations, owing to the tremendous increase in coronary flow. The same holds good for pulmonary pressures.[74] Katz and I[75] demonstrated, however, that similar reactions do occur in the intact circulation when neither venous pressures nor pulmonary pressures alter. By means of optically recorded aortic pressure and ventricular volume curves we showed that the ejection period tended to be reduced, but that the velocity of ejection increased. How this comes about can be analyzed better by registration of ventricular pressure curves, for we are confronted with a cardiodynamic situation in which the left ventricle contracts against a larger afterload and is stretched during diastole, whereas the right ventricle continues to operate under approximately normal conditions in the body. These details have been analyzed elsewhere.[67]

Similar reactions apparently occur in human hypertension, for evidence shows on the one hand that systolic discharge is essentially of normal magnitude,[18, 19] whereas total systole and the ejection phase are generally increased slightly as long as the heart remains competent.[76, 77] Evidence is at variance as to whether duration of isometric contraction increases or decreases slightly.[76, 78]

Cardiac Work.—It is easy to prove by the application of simple equations ($W = QR + \frac{WV^2}{2g}$, Evans[79]) in which changes in kinetic energy of flow (second factor) are disregarded, that the work of the left ventricle is augmented. The probable increase in the case of the human heart when pressures rise from 120/80 to 240/130 mm. Hg was estimated as about 95 per cent by Fahr,[80] who used the potential energy factor (first) of the equation, $W = \left.\begin{matrix} Ps \\ Pdv \\ Pd \end{matrix}\right\} + \frac{SV^2}{2g}$, and the distensibility curve of mean normal arteries given by Bramwell and Hill.[62] Similar conclusions were reached in case of experimental animals by Straub,[81] who constructed geometric work diagrams from simultaneous pressure and volume changes of the heart. Both agree that the increase in work is nearly proportional to the elevation of systolic pressure and relatively much greater than the elevation of mean or diastolic pressure.

These calculations, in fact, fall short of the actual increase in left ventricular work since the considerable increase in velocity during systolic ejection is not taken into account, a point to which many investigators have appropriately called attention.

The Efficiency of Beat.—The efficiency of cardiac muscle may be expressed as the ratio, $\frac{\text{total energy expenditure}}{\text{work in kilogram-meters}}$. In the heart-lung preparation the latter can be calculated from oxygen consumption, and this is readily translated into kilogram-meters. In this way the normal efficiency has been estimated at 20 to 28 per cent, under varying conditions, by Evans.[79] It seems to have been definitely established that not only is the oxygen consumption increased almost in proportion to the elevation of arterial pressure, but that the efficiency of contraction is slightly improved.[19, 82] Evans and his co-workers[83] suggest that this increased energy may be derived from oxidation of lactic acid, and that the latter may be partly responsible for the increased efficiency.

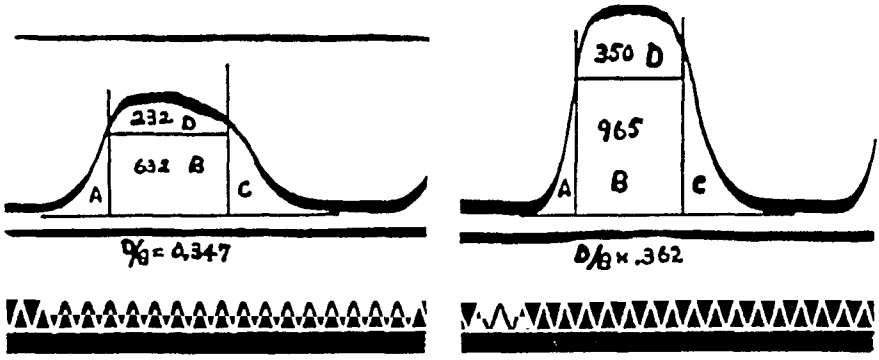

Fig. 8.—Two curves showing the effect of increasing arterial resistance on intraventricular pressure of dog, and the method of Wiggers and Katz for comparing the economy of effort as ratio, $\frac{\text{area } D}{\text{area } B}$. Note that no significant differences in D/B ratio exist. Discussion in text.

Unfortunately, such estimates of efficiency are not applicable to the intact animal and even less to man. Hence, we know almost nothing as to how economically the heart operates when hypertension is maintained, and whether subsequent development of hypertrophy improves or impairs the efficiency of its beat.

With the probability that a relationship exists between the efficiency of contraction and the economy with which mechanical energy developed is utilized, Katz and I[84] compared the static and dynamic efforts of the heart beat during ejection by analysis of tension-time relations in ventricular pressure curves. The idea may be expressed by the following analogy:

Suppose an individual desires to throw the contents of a pail with some force over a high wall. Such an act would require an initial and sustained energy expenditure in raising the pail above the level of the

wall and of holding it at this height (static effort), plus additional energy required to throw its contents over the wall (dynamic effort). Similarly the heart expends energy in the static effort of elevating pressures to aortic diastolic levels and of maintaining such a level during ejection. The pressure energy developed over and above this during ejection is immediately utilized to overcome resistance and maintain systolic flow, and the remainder becomes converted into energy of flow during diastole, i.e., potentially it represents dynamic effort.

The left intraventricular pressure curve is enlarged, copied, and divided into four areas labeled *A*, *B*, *C*, and *D*. This is illustrated on

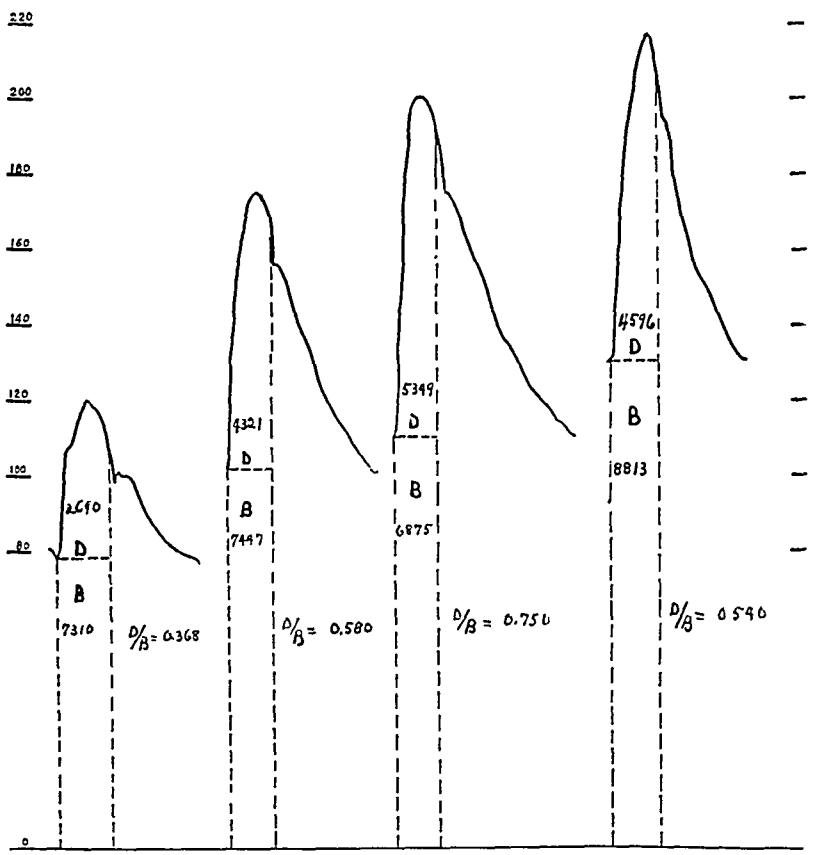

Fig. 9.—Pressure pulses from same patients as those of Fig. 5 and 7, illustrating method for calculating economy of effort on patients as the ratio, *D/B*. Note the great improvement in utilization of the energy released, as denoted by increase in ratio, *D/B*.

original curves in Fig. 8. Areas *A* and *C*, measured with a planimeter, represent the static efforts required during isometric contraction and relaxation, respectively. Areas *B* and *D*, marked off under that portion of the curve representing systolic ejection, are respectively considered to be indexes of the static and dynamic efforts during ejection, because area *B* represents the pressure energy required to sustain the blood column at a diastolic level, and area *D* represents the energy which is convertible into energy of flow. Since changes in the capacities which occur

from moment to moment in the ventricle affect both areas equally and simultaneously, the ratio $\frac{\text{area } D}{\text{area } B}$ expressed the economy of effort.

The two curves reproduced in Fig. 8 show at a glance that as soon as the heart compensates as a result of a greater diastolic size and initial tension (i.e., during the second stage described above), area *D* increases relatively more than area *B*. Occasionally this restores the quotient to normal, hence the deleterious effects of an increased afterload are neutralized. The heart never overcompensates, in the sense that the quotient becomes greater than normal.

Such reactions on animals are merely indicative of what may occur in man; they do not take into account unknown adaptive mechanisms that can be introduced in persistent clinical hypertension. With the hope of comparing the economy of effort in patients with hypertension and normal subjects, Dr. Wright and Dr. Hallaran are engaged in an attempt to apply the method clinically. The basis of comparison consists in obtaining good subclavian arterial pulses and considering the systolic and diastolic pressures obtained from the brachial artery as the ordinate values of such curves. Since these curves may be regarded as the summits of intraventricular pressures, the areas *D* and *B* (Fig. 9) can be determined by dropping perpendiculars to an arbitrary zero level. Results in process of publication leave no doubt that, as shown in these curves, the efficiency with which the ventricle utilizes the energy is far above normal in human hypertension.

The Cardiac Reserve.—While the efficiency of beats in patients with hypertension seems to be increased, we must not lose sight of the fact that the hearts of such patients are continually working nearer their limits of cardiac reserve. If volume curves of the ventricles are recorded in experimental animals while the venous return is progressively increased during acute hypertension (Fig. 10), the records show that the ventricles dilate progressively and that the systolic discharge increases up to a certain point (*C*), but beyond this decreases. This illustrates in a simple way the reactions to increased stretch, regardless of how it is produced, including such conditions as hypertension, aortic lesions, etc. The region of the curve *BC* represents the reactions termed compensation; the regions *CD*, those variously designated as cardiac failure or decompensation.

Now since the normal heart operates in a region to the left of *A*, any further increase in diastolic distention through augmented venous return, such as is produced by muscular exercise, for example, causes a compensatory increase in systolic discharge (*AC*). If, however, as in severe valvular lesions or hypertension, the heart is already operating in the region *AB*, a similar or even smaller increase in venous return, due to exercise, at once shifts the reactions of the ventricles to the areas *BD*; in other words, temporary decompensation occurs. This explains

the limited capacity of such individuals for exercise and the development of an effort syndrome upon exertion. Another way to express these thoughts is that normally the shift of cardiac reactions upon exertion to *AB* or *BC* brings the cardiac reserve power into action; but in hypertension the ventricles are already operating in the field of cardiac reserve, *BC*, and further dilatation shifts their reactions beyond this field, i.e., into area *CD*. Such analysis ought to give a clearer meaning to such commonly used terms as cardiac reserve, compensation, and decompensation.

The Coronary Flow.—Since, during hypertension, the total energy exchange, as well as the work of the ventricle, increases very nearly as the systolic pressure, provision ought to exist for a correspondingly aug-

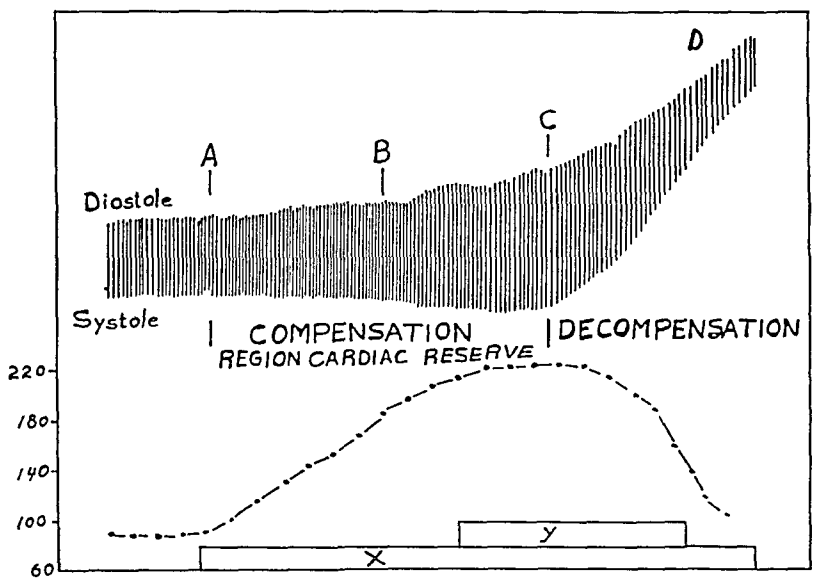

Fig. 10.—Plot showing changes in upper curve in diastolic and systolic volumes and in systolic discharge and in lower curves, changes in mean pressure during stimulation of pressor fibers in vagus nerve, *(X-X)*, and during added infusion of 300 c.c. saline *(Y)*. Discussion of phenomena of cardiac reserve, compensation, and decompensation in text.

mented coronary flow. Indeed, sclerosis of the coronary arteries, unless compensated by improved collateral flow, must soon lead to cardiac failure.

Three distinct views exist as to the manner in which coronary flow is adapted to the work of the heart, viz., (1) that changes in aortic pressure play the dominant role, (2) that mechanical adaptive reactions between coronary resistance and arterial pressures are automatically brought into play, and (3) that chemical products of metabolism or nervous reflexes enhance coronary flow by dilating the coronary vessels.

The dominant role of aortic pressure in determining coronary flow has been established, but differences of opinion exist as to whether it increases with mean or diastolic pressures.[85] Since hypertension in-

volves an increase in the vigor of ventricular contraction and sometimes changes in heart rate as well, we cannot apply unreservedly conclusions reached under general conditions of coronary flow. This is particularly true since recent investigators hold contrary views regarding the effects of increased force of contractions, viz., (a) that they favor flow by massaging effects, or (b) reduce flow by greater compression of intramural vessels during systole.[85] Green, Gregg, and I[86] devised a method by which relative changes in systolic, diastolic, and cyclic flow could be compared in the same animal, although no absolute values for flow can be deduced. It consists essentially in recording simultaneously pressures in the central and peripheral ends of the ramus descendens anterior, subtracting the values of the latter from the former at consecutive points, and thus deriving a velocity curve. The areas under such curves express in arbitrary units the relative systolic and diastolic volume flows, and the sum of the two equals flow per beat. By studying changes in the same animal during hypertension, Gregg[87] found that the increase in flow is definitely greater than the rise of systolic pressure. Detailed analysis of curves showed that although systolic flow is somewhat increased, diastolic flow is especially augmented. The former occurs because the coronary resistance increases relatively less than aortic pressure during ejection, whereas the latter is chiefly due to elevation of pressure during diastole. The conclusion was thus reached that mechanical adaptations are quite adequate to insure the necessary improvement in coronary blood supply during hypertension. Nervous reflexes seem to act in just the opposite direction, for aortic and sinus caroticus reflexes induced by hypertension are said to diminish coronary flow.[88, 89] Since these reflexes were operative in some of Gregg's experiments, as indicated by slowing of the heart with increased tension, it can be said that the mechanical adaptation is much the more potent in adapting blood flow to cardiac work. Inasmuch as hypertension seems to increase coronary flow reflexly, it would seem, teleologically, that these reflexes serve their chief purpose in improving the blood supply of the heart under such conditions as shock, hemorrhage, dynamic failure of the ventricles, etc., in which the fall in pressures might otherwise cause serious impairment of coronary flow.

SUMMARY

1. Persistent experimental as well as human hypertension is probably due, fundamentally, to the operation of humoral agents, but nervous mechanisms may be temporarily or permanently active in addition.

2. The dynamic resemblances and differences between experimental and clinical forms of hypertension deserve further study by apparatus more suitable for recording pressures in animals, and the results require better integration with changes in heart rate.

3. The concepts of "central," "collective" and "effective peripheral" resistances are analyzed, and formulas for mathematical calculation of the latter are given.

4. Calculations of peripheral effective resistance by several formulas show that it is increased in various forms of human hypertension. But the magnitude of the increase does not necessarily correspond to the degree to which mean blood pressure is elevated, suggesting that other mechanisms are also concerned.

5. Old and new experiments are reviewed which demonstrate that an intensive narrowing of small vessels in the splanchnic area must occur in order to produce elevations of pressure equal to those found in hypertension. Evidence is lacking that constriction of limb vessels contributes essentially to the height of pressure in animals or in man.

6. Organic lesions are not generally distributed widely enough to account for the increased effective resistance, and there are good grounds for questioning whether significant narrowing occurs in restricted areas during life. The view that functional contraction of arterioles and prearterioles occurs is plausible, but we must not be too dogmatic in assigning the increased resistance entirely to arteriolar regions of the arterial tree. Some of the resistance may occur in vessels larger than prearterioles.

7. Diminished elasticity of the aorta and its immediate branches accentuates the elevation of systolic pressure and reduces the diastolic pressure. It accounts also for the large pulse pressure and the rapid diastolic decline of subclavian pulses in hypertension. The absence of a significant increase in diastolic pressure, far from denoting inconsequential involvement of peripheral vessels, is probably more often a sign of an extension of vascular changes to the larger vessels. It is questionable whether the division of cases of human hypertension into systolic and diastolic types serves any useful purpose.

8. Although sclerosis of larger vessels produces such changes, the suspicion has existed that aortic distensibility is also decreased, even when no pathologic changes are demonstrable. The view that in such subjects the aortic distensibility is decreased beyond that common for corresponding ages is supported by considerations arising out of new experiments on circulation models, on the perfused dog's aorta in situ, and by simultaneous records of aortic pressures and diameters in living dogs.

9. Studies of pulse velocity are not destined to supply practical proof of the involvement of larger vessels in man owing to the difficulty of measuring arterial distances with sufficient accuracy.

10. The hypothesis is suggested that the agent or agents that are concerned in the production of experimental and human hypertension tend to act along the entire arterial tree, causing contraction of the muscular elements. In the smallest peripheral vessels this narrows the lumen and

increases peripheral resistance; in the aorta and distributing branches it reduces capacity and extensibility.

11. Physiologically, the action of the left ventricle is not impaired as a result of the greater work imposed upon it by severe hypertension. In animals the output tends to increase, the mechanical efficiency is increased, and the economy with which the mechanical energy is utilized to propel blood is decidedly increased.

12. In order to do this the ventricle operates continually in the region of cardiac reserve, and if additional distention occurs, e.g., because of an added return of blood, as during exercise, it responds with decreased, rather than, as normally, with increased output. This explains the limited capacity for exercise and development of the "effort syndrome" on exertion.

13. Recent experiments in which changes in coronary arterial inflow under natural aortic pressures were studied by differential pressure curves indicate (1) that coronary blood flow increases as the systolic pressure, and (2) that mechanical adaptations between peripheral coronary resistance and aortic pressure, rather than nervous reflexes or chemical actions, are chiefly concerned.

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THE TREATMENT OF ANGINA PECTORIS BY METHODS WHICH APPEAR TO PROMOTE MORE ADEQUATE FILLING OF THE HEART*†

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IT IS generally agreed that anginal pain is related to myocardial ischemia or relative anoxemia.‡ The secondary metabolic changes in the myocardium presumably result in products which stimulate nerve endings, giving rise to symptoms grouped under the syndrome of angina pectoris. If these statements are true, we should expect that circumstances restricting the blood flow in the coronary circuit generally, or locally in relation to work done by the myocardium, would give rise to symptoms. In middle life or beyond, structural changes at the orifices or in the walls of the coronary vessels produce local barriers to the free passage of blood to certain parts of the myocardium. If these vessels retain their function of varying the caliber of the lumina, there will be circumstances when the flow may be increased or decreased in these areas, thus adding to or subtracting from the impediments of structural narrowing. The variability of function of the anastomosing branches from the remainder of the coronary vessels likewise influences the blood supply to the restricted areas.

If we list the functional disturbances predisposing to anginal pain, we shall find grouped under these headings most of the common clinical examples encountered in practice. The list by no means exhausts the possibilities suggested by this approach to the subject. Most of the forms of functional disturbances and the representative clinical types are obvious and have been mentioned by recent authors. The last group is, at the moment, hypothetic, but ultimately may be found to contain the great majority of patients presenting the anginal syndrome. It is this group with probable faulty filling of the heart and, secondarily, inadequate filling of the coronary vessels which is of particular interest.

For several years we[1] have observed and treated an increasing number of patients who presented a clinical syndrome of obesity and postural

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‡What is said concerning the myocardium may apply, likewise, to the base of the aorta, which is supplied by branches of the coronary arteries.

emphysema with variable circulatory symptoms, who, in addition, complained of symptoms related to disturbances in the spinal column, with radiculitis, who had symptoms associated with increased load and trauma on the weight-bearing joints, and who showed signs of hernias resulting from stresses on the abdominal wall. Many of these patients were referred to us originally because of the characteristic components of anginal pain.

Most of the patients were in the sixth or seventh decade of life, and a small group were in the fifth decade. In appearance, they were of the type generally spoken of as apoplectic, with florid complexion and moderate or marked corpulency. They complained of orthostatic dyspnea, i.e., they had dyspnea only in the upright position and could lie supine without discomfort. The spinal curves were all exaggerated, and there was marked lumbar lordosis, moderate or marked upper thoracic kyphosis, and an increased cervical lordosis. The exaggerated curves of the spinal column assisted the individual to "get under" the great weight of the protuberant abdomen. Under these circumstances, the lower ribs were shown to be in the inspiratory position, and the upper ribs in front were approximated and relatively fixed in the expiratory position. With the patient standing before the fluoroscope, the diaphragm was found to be one or two interspaces below the normal position; in ordinary breathing with the patient in the upright position the movements were limited, but when the patient was supine the diaphragm had a much greater excursion. It was assumed that the abdominal viscera together with the increased accumulation of fat served as a counterweight suspended from the diaphragm. When the patient was in the upright position, this weight interfered with the normal rise of the diaphragm during expiration, but when the patient was in the supine position it caused the diaphragm to rise higher in the chest during expiration and acted as an aid to respiration. The relaxation of the fascial sheet extending from the cervical fascia to the lumbar spine, and including the pericardium and central tendons of the diaphragm, also interfered with the normal movements of the diaphragm. It was apparent that the diaphragm, handicapped by the counterweight, the flared lower ribs, and the relaxed anchorages, was unable to maintain the tidal air at the normal level, and this probably explained the orthostatic dyspnea. Likewise, the resulting pulmonary emphysema seemed to be the cause of moderate polycythemia.

When studies were begun on this group several years ago it was obvious that some attempt should be made to improve the respiratory functions. Two therapeutic procedures were adopted: (1) A belt was devised[1, 2] which had two qualities: it was strong because it was designed to lift the counterweight, and elastic to permit expansion during inspiration and to assist in elevating the diaphragm during expiration. (2)

A reducing diet was prescribed to bring the patient's weight to a more normal level over a period of several weeks or months.

The results from the treatment of this group of patients have been very gratifying, as we have reported previously. During the past four years, I have been impressed with one result in a number of these patients that was wholly unexpected and, I think, unique. One after

TABLE I

FUNCTIONAL DISTURBANCES	AGENTS OR CLINICAL STATES
Effects of vasoconstricting drugs	Adrenalin Nicotine Ergotamine tartrate
Functional state causing vasoconstriction	Exposure to cold Alkalosis with tetany, associated with the anxiety states (hyperventilation) ? Effort syndrome Painful stimuli
Reduction of oxygen-carrying capacity of the blood	Severe anemia—relation of angina pectoris to primary or posthemorrhagic anemia; relief after restoration of the blood to normal levels Reduction of the level of red blood cells in polycythemia vera and in polycythemia associated with pulmonary emphysema Anoxemia caused by anesthetics Anoxemia in carbon monoxide poisoning
Fall in the level of systemic blood pressure	During sleep, in shock, in myocardial failure Aortic insufficiency with low diastolic pressure
Increased work of the heart	In hyperthyroidism, relieved by proper treatment During exercise, relieved by rest and vasodilator drugs Effects of thyroid extract in myxedema in older persons
Decreased filling of the heart and secondarily reduced filling of the coronary vessels	Paroxysmal tachycardia or shortening of diastolic phase from other types of tachycardia Postural hypotension Faulty movements of the diaphragm through counterweight of fat on viscera and after meals Organic obstruction of vessels returning blood to the heart

another of the patients who originally came complaining of anginal pain reported complete relief from this symptom. This relief began almost at once after the elastic belt was properly applied, and therefore was not caused by reduction in weight. The same result could perhaps have been obtained by reducing the counterweight in the abdomen through general reduction in body weight, but only after weeks or months of dietary restriction. These patients found that they had no further need for vasodilator drugs; and whereas formerly they could walk but short,

measured distances without pain, soon they could go long distances and even up inclines without any components of anginal pain whatsoever. To date I have seen approximately one hundred patients with typical symptoms of angina pectoris who have been treated in this manner, and the results have been uniformly excellent.

An exact explanation of the results described must await further study. It is believed that restored function of the diaphragm may be an important factor. In breathing, the movements of the diaphragm aid the return of blood to the heart through alternating changes in the intrapleural and intraabdominal pressures. With the patient in the upright posture, the relatively inactive diaphragm may materially impede the flow of blood from the abdominal viscera and the lower part of the body. It has been demonstrated in the patients with circulatory symptoms that in the upright position the blood and pulse pressures in the arms are very much lower than in the supine position. In some cases, no satisfactory auscultatory readings of arterial pressure could be obtained in the arms when the patients were in the upright position. There was very little difference in readings whether the arms were held horizontal or dependent. Studies on the circulation time and other studies have been started in order to find, if possible, the location of the alteration in function which relieves the pain.

SUMMARY

A brief report of observations on the relief of anginal pain, obtained by improving the movements of the diaphragm and presumably acting through more adequate filling of the heart and coronary vessels, is submitted. A positive means of prevention and treatment of anginal pain in the group of patients who are potential or actual sufferers from the syndrome is offered in the form of an elastic abdominal support supplemented by dietary restriction. It is probable that by these means the common catastrophe of coronary thrombosis may be postponed. While the great majority of persons who suffer from angina pectoris are obese, we have noted that a lighter type of elastic belt affords complete relief to the few individuals of slender build with the same syndrome. The elastic belt obviously can be of no value if the diaphragm is fixed through disease.

At the moment, the methods described would appear to be of distinct value to those who appear with well-established symptoms. However, if we are to prevent or postpone the development of the syndrome, we must apply this knowledge to the large group of sedentary workers, chiefly males, who are given to indulgence in good food beyond their needs. If our experience is duplicated by that of other clinicians, the way may be found to lessen the mounting toll of deaths in this group during middle life and beyond.

It is suggested that this approach to an understanding of problems concerned with the coronary circulation will have an application in the study of the arterial supply to other organs, especially to the brain, which in patients in this group is likely to be the seat of vascular accidents.

At a later date case histories and details of the studies that are now under way will be reported.

These remarks are dedicated by kind permission to Dr. James B. Herrick.

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VASCULARIZATION OF ATHEROSCLEROTIC LESIONS*

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RECENTLY much attention has been given to the vascularization of atherosclerotic lesions. Inferences have been drawn with reference to vascularization which do not appear to be justified from careful studies of the material.

THE CIRCULATION TO NORMAL ARTERIAL WALLS

The literature on this subject has been reviewed recently by Ramsey.[1] The general opinion of investigators is that vasa vasorum supply the adventitia and the outer third or outer half of the media of the human aorta. The nutrition of the intima is cared for by diffusion from the lumen. The inner portion of the media may be supplied by diffusion from two sources, the lumen and the vasa in the outer portion of the media. Much of the work reviewed by Ramsey was carried out in the last century. Subintimal vessels from the vasa were reported in the aorta of the cow and the whale,[2] in the human fetus, and in undernourished infants.[3] However, the evidence produced, even by believers in the theory that vasa vasorum supply the nutrition of the adult human intima, is feeble or lacking. Koester,[4, 8] who originated this theory, based it on the reasoning that all tissues should have a circulation. This overlooks the fact that the cornea and the adult lens, placed under conditions less favorable for nutrition than the arterial intima, are avascular. Efforts to demonstrate the presence of any vessels (blood or lymph) in the intima of normal human arteries have failed, save for rare questionable single vessels, even though the injection medium was a solution of nitrate of silver and not a suspension of pigment. The silver nitrate method failed also in the cornea.

Among recent papers on the subject of the circulation to arterial walls is that of Woodruff,[5] who injected India ink gelatin into the aortas of the horse and the dog and also injected vasa vasorum directly through specially devised glass cannulae. Vasa vasorum in the horse penetrated all layers of the media but terminated abruptly at the intimal junction. The general source of the vascular supply to the aortic walls in both the horse and the dog was from vasa vasorum arising from aortic branches. However, he found in 20 of 21 dogs that some vasa vasorum arose in the ascending arch directly from the aortic lumen and that these were distributed to the media. The number of vasa derived from the aortic lumen varied from one to seven. In the dog which showed no such vessels, the aorta was the seat of sclerosis. No circulation to the intima was disclosed in these studies.

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Robertson,[6] using for injection stable suspensions of pigment and radiopaque material, found discrete openings in the ascending aortas of two dogs. In two sections from human aortas minute nutrient vessels were seen penetrating the intima and branching in the inner third of the media. From studies of the aortas of the dog, the lamb, and man he concluded that the thoracic aorta is vascularized by a sheath of areolar connective tissue, richly supplied with vessels derived from the vessels of adjacent structures or from branches of the aortic efferent vessels, and forming an anastomosing network. The richest portions of this network were found about the arch and about the orifices of aortic branches. Vasa penetrated no further than the outer third of the media. Even the exceptional two minute vessels arising from the lumen of a human aorta were distributed to the inner third of the media. The *intima, without exception, had no vascularization in normal aortas.*

POSSIBLE RELATION OF THE LOCALIZATION OF ATHEROSCLEROTIC LESIONS TO THE DISTRIBUTION OF VASA VASORUM

Raynaud[7] in 1865 and Koester[8] in 1876, followed by many others, concluded that there was a relation between the vascular supply to the vessel wall and the localization of atherosclerotic lesions. Klotz in several studies supported this thesis. He demonstrated that syphilitic aortitis apparently owed its origin to infection extending along the lymphatics which accompany the vasa vasorum into the aortic wall.

The preferred localization of syphilitic aortitis, the ascending aortic arch, is in a region richly supplied with vasa vasorum. However, though the ascending arch is frequently the site of multiple, early, so-called pinhead atheromas, it is not a common site of advanced atherosclerotic lesions, except when these are engrafted on lesions of syphilitic aortitis. The early atherosclerotic lesions in this location tend to remain small and focal. The rich cholesterol deposits in these multiple pinhead lesions are removed by a mechanism which I have described[9]; the lesions subside and disappear, leaving a smooth intima without evident scarring. It should also be remembered that syphilis is an infection, whereas the lesions of atherosclerosis have at least no direct relation to infection.

Robertson concluded that a relation exists between the presence of certain lesions of the aortic wall and the distribution of the vasa vasorum. The richer the anastomosing network of vasa in a given locus, the greater the likelihood that lesions of the vessel would arise in that locus.

In a study of the very frequent localization of arteriosclerotic lesions about the orifices of the intercostal arteries, Klotz[10] argued that the mechanical theory of causation is wholly inadequate to account for this distribution of lesions, particularly when it is recognized that the intercostal orifices arise along the best supported portion of the aorta. Discussion of this question, however, should take into consideration that not only is the posterior wall of the aorta the best supported portion, but it is also for the same reason the portion of the wall which is relatively

fixed—anchored—by the intercostal vessels, while the rest of its circumference is comparatively free. The ascending arch of the aorta is the only portion of the vessel which is without branches and is unconfined. It is also the portion of the aorta, as indicated, which is least commonly the seat of advanced atherosclerotic lesions. The muscle waves of contraction and expansion of the aortic wall are unhampered in the free and branchless portion of the arch, but must meet with interruption about the orifices of vessels. Moreover, the interruption should be greatest about the orifices of those vessels which promptly enter fixed tissues, and permit little or no movement of the aortic wall, as is true of the intercostal arteries. That stresses due to interruption of the muscle waves are a factor in localization of atherosclerotic lesions is suggested by the frequent occurrence of lesions about the orifices of all of the aortic branches.

The atherosclerotic lesions about intercostal orifices are outstanding because once established they tend to be permanent. The common lesions of the ascending arch are as a rule temporary and disappear even at advanced ages, leaving little or no evidence of their presence. Lesions about intercostal orifices usually progress to the stage of permanent scarring and persist during the lifetime of the individual.

Klotz realized the futility of studies of advanced lesions in any effort to determine the etiology of arteriosclerosis and focused attention on the more informative early lesions. Atherosclerosis begins in the most superficial layers of the intima, in the region farthest removed from distribution of the vasa vasorum. It is difficult to understand how anything connected with the circulation through the vasa could influence the localization of such lesions. Klotz, from his study of early lesions, particularly in young persons who had died of infections, recognized this limitation and concluded that reactions in the intima, in many infectious diseases, may occur independently of, although simultaneously with, the inflammatory reactions about vasa vasorum. Animal experiments, in his hands, gave inconstant results.

MacCallum[11] concluded from his studies that: "It appears that there is but little evidence in favor of the idea that infections, whether acute or chronic, play a part in the pathogenesis of arteriosclerosis."

My studies of early lesions of atherosclerosis disclose that the process is not inflammatory in origin. Inflammatory cellular infiltration is absent in the earliest lesions and only rarely can a lymphoid or plasma cell be found in the early stages as the lesions enlarge and extend. When necrosis occurs, inflammatory cellular infiltration becomes common.

We may conclude, therefore, that materials of infectious origin which might be carried in the blood of the vasa vasorum play a minor part, if any, in the etiology of arteriosclerosis, or in the localization of lesions.

THE ORIGINS OF INTIMAL CIRCULATIONS IN ATHEROSCLEROTIC LESIONS

Just as the normal intima has no circulation, a careful study which I made of a large series of early atherosclerotic processes demonstrated

that these lesions also have no circulation. Only as the lesions enlarge beyond the early stages does a circulation appear. On the other hand, a study of over 200 advanced coronary lesions from 120 cases of coronary sclerosis disclosed that all advanced lesions are vascularized. It was intended to carry this study through a much larger series of coronary vessels, but the constancy of the findings (not a single exception) made this unnecessary. The laws of nutrition and growth govern this as they do all other reparative processes.

As we have seen, diffusion through the endotherial lining furnishes the nutritive support for the intima and in part at least the inner portion of the media. The nutrition of the early lesions of atherosclerosis is likewise cared for by diffusion. As the lesions enlarge, and particularly if fibrosis occurs, there comes a stage at which nutrition by diffusion is no longer adequate. Necrosis of the deep layers of the lesion, i.e., those farthest removed from the lumen, the source of nutrition, is practically constant. If the lesion is to enlarge beyond this stage, a new source of nutrition must be supplied and is provided through vascularization. The new vessels may originate from two possible sources. In the young particularly, new vessels may arise directly from the lumen, as I first reported.[12] Apparently, the distribution of these vessels may be limited in some cases to the diseased intima. Or, particularly in older persons, the new vessels may arise from vasa vasorum which penetrate through the inner layers of the media to reach the atherosclerotic nodules in the intima. The formation of these new vessels to the intima from either source is a late phenomenon, occurring only after the lesions as they enlarge have exhausted the possibilities of nutrition by diffusion.

Winternitz, Thomas, and Le Compte have revived the question of possible vascularization of the normal intima in a paper entitled "Studies in the Pathology of Vascular Disease."[13] They indicate that they are presenting new knowledge which will aid in the understanding of the anatomical processes involved in atherosclerosis. They deprecate the value of contributions concerning the pathology of the various processes, which have proved disappointing.

"Present day descriptions of the process differ in no essential from those of Morgagni save that they are more brief and employ a somewhat changed nomenclature. The histological picture and its interpretation is not different from that of the time of Virchow." It is evident that the authors of this paper are lovers of the older medical literature. There is only one reference to a modern study on atherosclerosis in their short bibliography. Morgagni died in 1771. Virchow died in 1902. Aschoff and the modern German school, Anitschkow and the Russian school, Klotz and MacCallum and the American school have added at least some data in the decades which have elapsed since Virchow's death.

The embryological work of Bremer[14] is referred to as establishing the developmental basis for a vascular pattern such as is found in the aorta of the cow. In this animal small vessels arise from the lips of the

branches, and coursing *under* the intima anastomose with minute vessels arising from the lumen. Winternitz and his associates agree that this pattern is difficult to show in all human arteries. "Frequently, however, in the coronaries and in the abdominal aorta very minute vessels are encountered arising independently from the wall and running to the adventitia where they anastomose in the rich adventitial plexus. Occasionally such vessels, as they penetrate the aorta, are seen to give off small branches to the intima and media. After examination of many human arteries it must be emphasized that vessels are seldom demonstrable in the intima or in the inner half of the media when no irritative, obliterative or morbid process is present." The last sentence indicates that the lesions on which this paper was founded were advanced lesions. Atherosclerosis and its effects are the commonest and most important agencies responsible for irritative, obliterative or morbid processes in the arterial intima, excluding syphilis and the repair at the site of the ductus arteriosus orifice. How the study of advanced lesions can be very helpful in determining the etiology of atherosclerosis is difficult to comprehend.

The authors of this paper endeavor to emphasize the importance of hemorrhages through rupture of the delicate vessels found in the lesions. One gets the impression that hemorrhages are early phenomena and etiologically important in atherosclerosis. An interesting demonstration of the translucency of the normal aortic intima can be made by injecting minute drops of oxalated blood into the intima or the subintimal media. If the hypodermic needle is thrust diagonally through the back of the aorta the blood may be placed with some exactness. The specks or colored hillocks of the injected blood could not be overlooked even by a tyro in pathology. Atherosclerosis is perhaps the commonest chronic human disease; the aorta is a favorite site for localization of its lesions, and yet such hemorrhages into the normal aortic intima have not been reported. A marked increase in the thickness and opacity of the intima could be the only means of cloaking such a hemorrhage from view, and this type of change could be produced only in advanced lesions.

An effort is made to account for the cholesterol found in atherosclerotic lesions as arising from the blood of these hemorrhages. "It is reasonable to suppose, therefore [i.e., because of the accumulation of fatty material at the site of a hemorrhage], that this fatty material is derived from, and eventually replaces, the blood of the original hemorrhage," etc. Normal blood contains not more than 820 mg. of total fats per 100 c.c. of blood, less than 1 part in 100. But it is agreed that most of the fat in atherosclerotic lesions is cholesterol. Normal blood contains not more than 230 mg. of cholesterol in 100 c.c., less than 1 part in 400. It is hardly reasonable to suppose that fatty material present in blood in these minute amounts could replace the blood of the original hemorrhage or account for the massive collections of cholesterol found in atherosclerotic lesions. It is generally agreed that the cholesterol in

these lesions is transported to the site of the lesions either in macrophages or free in the blood stream, and does not arise locally from hemorrhages.

Notwithstanding the claims of Winternitz and his co-workers, it must be concluded that:

1. The normal intima is not vascularized, and that intimal vessels are found only in connection with vascular lesions in which repair has taken place.

2. Since the vessels arise as the result of repair processes, i.e., since the lesions are advanced atherosclerotic lesions, the hemorrhages from such vessels must be late phenomena and are, therefore, not of etiologic importance.

3. Cholesterol found in atherosclerotic lesions is transported to the site in macrophages or as free or ester cholesterol in the blood, and does not arise locally except perhaps in small amounts.

4. The laws of nutrition and growth still hold in atherosclerotic lesions.

Finally, to quote Klotz on the etiology of atherosclerosis: "It may be well to indicate that the mode of origin or the previous course of a fully developed plaque of endarteritis cannot be determined by a study of the old lesions alone, and it is futile to hold controversy over such an undeterminable problem. A study of the earliest stages of the lesions in the tissues of man is still the most secure upon which to base conclusions."

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THE USE OF METRAZOL IN COMPLETE HEART BLOCK WITH ADAMS-STOKES SYNDROME

Report of Four Cases

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COMPLETE heart block is infrequently encountered in medical practice; yet its presence always attracts considerable attention, especially when it is associated with the Adams-Stokes syndrome.

At present there is no entirely satisfactory treatment of heart block and Adams-Stokes syndrome. A number of drugs have been suggested from time to time, each with its initial series of good results and, later, almost invariably with its disappointments. Atropine sulfate in doses of 0.3 to 1.2 mg. (1/200 to 1/50 grain) is most commonly used. Its untoward side effects, viz., dryness of the mouth, dilatation of the pupil and gastrointestinal distress, restrict its continuous use. More important is the number of cases in which it does not increase ventricular rate nor decrease the periods of syncope. Barium chloride has been successfully used by many.[1] However, toxic manifestations, such as extreme breathlessness, irregular acceleration of the ventricles, and signs of collapse, have followed the use of 60 mg. (1 grain) doses.[2] In periods of ventricular asystole epinephrine has been employed frequently.[3] Levine and Matton[4] used it effectively by direct injection into the heart of a patient who had ventricular standstill lasting five minutes. Small daily doses of epinephrine have often been helpful in reducing the number of Adams-Stokes attacks. The necessity of repeated hypodermic injections and the pronounced sympathetic effects are hindrances to the prolonged use of this drug. Ephedrine is often effective in terminating the syncopal attacks and increasing the ventricular rate,[5] but continued oral administration also causes wakefulness, flatulence, and anorexia, often prohibiting the further use of the drug.

In view of the many causes of heart block and Adams-Stokes syndrome, their not infrequent tendency to cease spontaneously, and the different medication suggested in the past, it is with some scruples that another drug is recommended, yet the writer's observation of the effect of metrazol prompts him to say that in some cases it is beneficial, and that it compares favorably with any of the other drugs now in use; it has the further advantage that in cases in which it is effective it may be used with no apparent untoward side effects for prolonged periods.

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Metrazol was given to four patients with complete heart block and Adams-Stokes seizures. Two of them were greatly benefited by the drug; in the other two it was of no value. Case 3 was that of a patient on the medical service of Dr. Don C. Sutton, and I am indebted to him for permission to study it.

REPORT OF CASES

CASE 1.—M. L., a white woman, aged 78 years, was first seen on April 19, 1933, during a typical Adams-Stokes seizure. She had her first syncopal attack in 1925, at which time a physician made a diagnosis of complete heart block. After several days of rest in bed she resumed her former activities and was without symptoms for two and a half years, when a second attack occurred. Much like the first seizure, it lasted a few hours; it was followed, after a year and a half of well-being, by a third attack. During the next year the symptoms progressed rapidly, and the first break in cardiac compensation occurred. Prolonged rest in the hospital reestablished compensation and provided electrocardiographic evidence of A-V block with a ventricular rate of 40-44 beats per minute. Her symptoms progressed slowly, and she was given camphor in oil, barium chloride, epinephrine, and, finally, atropine. The latter was the only effective drug; it reduced the number of attacks from 50 to 4 per week. On Feb. 8, 1933, a second failure of compensation with considerable peripheral edema was observed. Atropine sulfate was discontinued. Five weeks later compensation was partially regained, but the syncopal seizures were more numerous than before. Neither the oral administration of atropine sulfate in doses of 0.64 mg. (1/100 grain) every four hours nor subcutaneous injections of 0.8 mg. (1/75 grain) every three hours gave any relief, and toxic symptoms and unpleasant side reactions forced us to discontinue this drug. Epinephrine, ephedrine, barium chloride, digitalis, camphor in oil, and pituitary extract were similarly ineffective.

Physical Examination.—The respirations were deep, labored, and slow (5 per minute). There was moderate atherosclerosis of the peripheral vessels. The pulse was regular and full, and its rate was 36 per minute. The blood pressure was 178/138. The apex beat was diffuse and was located in the fifth left intercostal space at the anterior axillary line. The heart was enlarged both to the right and left; the borders were 5 and 13 cm., respectively, from the midsternal line. No murmurs were audible, and the heart tones were loud and distinct. A few moist râles were heard over the pulmonary bases posteriorly, the edge of the liver was 5 cm. below the costal margin, and a moderate amount of edema of the legs was present.

Subsequent Course.—Several subcutaneous injections of epinephrine (0.5 c.c. of a 1:1000 solution) were given without any apparent benefit. One cubic centimeter of metrazol was given subcutaneously, and her respiratory rate increased markedly within five minutes. The injections of metrazol were repeated every five minutes, and within thirty-five minutes she regained consciousness; her respiratory rate was 20 and her pulse rate 62 per minute. One tablet of metrazol was given every half hour for the next seven hours. At the end of this period she had continued to improve so much that it was decided to allow her to rest and sleep. She awoke refreshed, but her pulse rate had fallen to 48 per minute. One tablet of metrazol every hour when she was awake was given during the rest of the week. No syncopal attacks were seen, her pulse ranged from 50 to 74 per minute, and her compensation improved. This striking effect aroused our curiosity so much that atropine sulfate, in doses of 0.3 mg. (1/200 grain) every second hour, was substituted for the metrazol. Six hours after this change in medication the first

Adams-Stokes syndrome appeared. During the next four days the attacks increased in number and severity. Again the medication was reversed; metrazol was given, and atropine discontinued, but it was several days before she was free from syncope. Improvement continued, the pulse rate remained above 54 per minute, and she was free from attacks during the next week. She felt better and despite advice to the contrary she got up and did some housework. There were several mild attacks, and she went back to bed. After that she failed rapidly and died two days later.

CASE 2.—E. D. L., an 83-year-old widow, had been a resident of the Presbyterian Home of Evanston for more than twelve years, during which time she had had a systolic blood pressure of 200 mm. Hg. She was first seen on July 30, 1936, after she had fallen twice while attempting to dress herself.

Physical Examination.—The patient was a moderately obese woman with a considerable degree of atherosclerosis of the peripheral vessels. The heart was moderately enlarged to the left and the apex beat was localized just beyond the midclavicular line. The blood pressure was 220/94, and the pulse rate was 58. Otherwise the findings were normal. She was advised to rest more, put on a salt-poor diet, and given theobromine sodium salicylate in doses of 0.6 gm. (10 grains) t. i. d.

Subsequent Course.—A week later the heart rate fell to 48 per minute, and there were many vertiginous attacks. An electrocardiographic tracing showed complete heart block. She was given one tablet of metrazol thrice daily after meals. Within a few days the attacks disappeared, but there was considerable unsteadiness of her gait. The dosage of metrazol was doubled in an effort to relieve the ataxia, which was thought to be caused by atherosclerotic changes in the arteries of the spinal cord. After four weeks of this new regime she felt better than she had in the previous two years; she was free from attacks, could walk better, and her pulse rate was 62 per minute. Metrazol was discontinued for several days, whereupon the Adams-Stokes syndrome reappeared, and the heart rate fell to 44 per minute. After a two-week period during which she took metrazol tablets every four hours she regained her previous good status and the pulse rate rose to 60 per minute. Again, the metrazol was discontinued and atropine sulfate in doses of 0.3 mg. (1/200 grain) was given thrice, then four times, daily. During the second week 0.6 mg. (1/100 grain) was given q. i. d., but there were still occasional periods of syncope and the pulse rate was 48. The extreme dryness of her mouth forced us to abandon the use of atropine and return to metrazol, which has kept her comparatively free from the Adams-Stokes attacks for the past eighteen months.

CASE 3.—C. W., a 58-year-old Pole, entered the Cook County Hospital Feb. 18, 1935, complaining of attacks of dizziness and fainting. He had been in good health until 8 years before admission, when he had had a severe respiratory infection of undetermined nature. This left him somewhat weak, and there was some dyspnea on exertion. Later there were occasional periods of dizziness that lasted 20 to 40 seconds. They grew progressively worse, so that two weeks prior to entrance he was forced to give up his work as a machinist. He denied any venereal infection and used alcohol moderately.

Physical Examination.—The patient was a slender, somewhat anemic man who appeared to be healthy. The apex beat was just outside the nipple line, and a loud systolic murmur could be heard over the aortic area. The blood pressure was 168/82. There was moderate atherosclerosis of the peripheral vessels; the pulse rate was 36.

An electrocardiogram showed complete block with normal ventricular complexes and a ventricular rate of 40 per minute.

He was given one tablet of metrazol q. i. d. for four days, without any effect on his pulse rate. The dose was doubled for the next three days and trebled the next week. Then he was given 1 c.c. of metrazol subcutaneously every two hours for the next week. His ventricular rate varied from 32 to 40 during that time, and he did not improve. Atropine sulfate in doses of 0.3 mg. (1/200 grain) was given subcutaneously for the next week, and within one day's time he felt better and his ventricular rate rose to 64. After a week of this treatment his Adams-Stokes seizures disappeared. The following week he was given no medication, and the ventricular rate fell to 40 per minute. Large doses of metrazol, 4 tablets every two hours and 2 c.c. every two hours subcutaneously, were ineffective. He was then given atropine sulfate in doses of 0.6 mg. (1/100 grain) after meals, which afforded him such complete relief of his symptoms that he left the hospital with a ventricular rate of 66.

CASE 4.—W. H. S., a white man 76 years old, was admitted to the medical service of the Research and Educational Hospital July 2, 1938. For three years he had suffered transient attacks of syncope which had become progressively worse during the preceding four months; they occurred from three to ten times a day, lasted from several seconds to a few minutes, and sometimes were so severe that he fell.

Physical Examination.—The skin and mucous membranes were pale, and there was a coarse tremor of the tongue. There was moderate emphysema of the lungs which made it difficult to percuss the cardiac borders. A soft systolic murmur was heard over the aortic area, and the heart tones were distant. The heart rate was 24 per minute, and the blood pressure was 154/42. Marked atherosclerosis of the peripheral arteries was noted. There was diffuse enlargement of the prostate.

Laboratory Examination.—The erythrocytes numbered 4,100,000 per cubic millimeter; the hemoglobin was 12.2 gm. per 100 c.c.; the Kahn reaction on the blood was negative. Except for a nonprotein nitrogen of 59 mg. per 100 c.c., the blood was chemically normal.

Subsequent Course.—During the first twenty-four hours in the hospital the patient had three attacks of syncope approximately one minute in duration. These attacks were not preceded by an aura; no period of stupor followed them; the patient did not bite his tongue. An electrocardiogram taken July 5 showed an auricular rate of 50 and a ventricular rate of 22 per minute. At times there was marked auricular slowing and standstill. Metrazol was given in doses of 1 c.c. subcutaneously every three hours. A series of electrocardiographic tracings was taken before and after a single metrazol injection. They showed some increase in auricular rate. After several days of metrazol treatment both by mouth and subcutaneously, his condition was much worse with increased periods of stupor, so that the drug was discontinued. Epinephrine (1:1000) was given subcutaneously in 0.3 c.c. doses every three hours with almost immediate benefit. The next day 2 c.c. of metrazol were injected intravenously while a continuous electrocardiogram was being taken. A comparison of this record with a control tracing taken before the injection, as well as with those taken at five-minute intervals afterward, failed to show any changes. Later, epinephrine was again discontinued and atropine and ephedrine in full therapeutic doses were tried. His pulse rate fell to 20-28 per minute, and he again became stuporous, so that epinephrine had to be given. The latter improved his condition sufficiently to allow him to be transferred to a convalescent home two weeks later.

COMMENTS

Metrazol, or pentamethylenetetrazol, was first introduced by Hildebrandt,[6] who found that it had certain advantages over camphor. It is water-soluble, can be sterilized easily, and acts promptly after subcutaneous injection mainly by stimulation of the vasomotor and respiratory centers. Cardiazol, as metrazol is called in Europe, frequently has been reported as a successful remedy for circulatory collapse.[8] The careful animal experiments of Camp[7] failed to demonstrate any direct action on the heart, nor did a single intravenous injection of metrazol in a patient (Case 4) show any electrocardiographic changes. There are but few similar references in the American literature.[9] Recently it has been given in large doses (5-7 c.c. of a 10 per cent solution) intravenously in the treatment of schizophrenia over extended periods without any apparent ill effects, so that prolonged administration evidently is not harmful.[10] A probable explanation of the beneficial effect of metrazol in complete heart block with the Adams-Stokes syndrome is that it stimulates the vasomotor tone and respiration. No explanation is offered for the ineffectiveness of metrazol in the other two patients, except that similar observations have been noted wherein one drug was ineffective and others were effective. This emphasizes the statement that there is at present no single, entirely satisfactory treatment of heart block.

CONCLUSION

Metrazol was given to four patients with complete heart block and the Adams-Stokes syndrome. Two of them were greatly benefited by the drug and two were not. Apparently the action of metrazol is on the vasomotor and respiratory centers, not on the heart.

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lower extremities. The heart sounds were faint, and gallop rhythm was present. The blood pressure was 210/120. The liver extended about an inch and a half below the costal margin. Ophthalmoscopic examination revealed one small hemorrhage in each fundus.

The urine contained albumin (graded ++) and blood (graded +++, Meyer's test), together with a few casts. The erythrocyte count was normal. The blood urea nitrogen was 11.9 mg. per cent, the creatinine 1.0 mg. per cent, and the uric acid 5.2 mg. per cent. The total plasma protein was 5.77 per cent (albumin 2.71, globulin 2.55, fibrinogen 0.51). The urea clearance was 75 per cent of normal. The plasma cholesterol was 250 mg. per cent. The blood Wassermann and Kahn reactions were negative.

The patient was kept at rest in bed and given a salt-free diet of normal protein content. In addition, 200 c.c. of a 25 per cent solution of glucose were given intravenously on three successive days. No digitalis was administered. Within three days the urinary output began to increase, with a corresponding decrease in the edema. During the first ten days the patient's weight was reduced from 166 to 132 pounds.

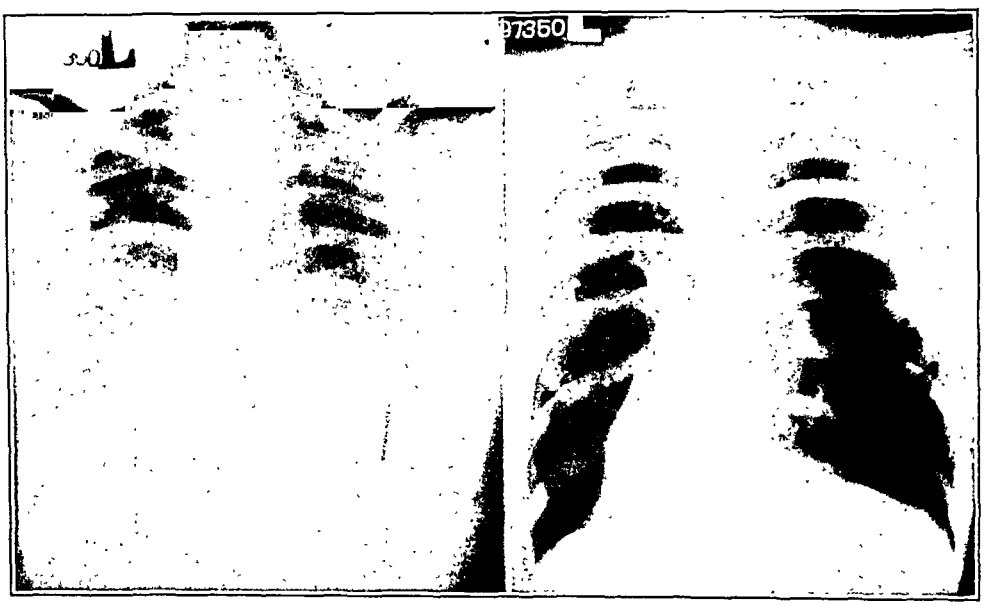

Fig. 1*A*. Fig. 1*B*.

A teleoroentgenogram made Oct. 3, 1935, the day after admission, revealed evidence of bilateral hydrothorax and passive congestion of both lungs (Fig. 1*A*); the heart was probably enlarged, but exact measurements could not be made because of the pleural effusion. The second teleoroentgenogram was made Feb. 19, 1936 (Fig. 1*B*). At this time the size of the heart was normal (Danzer ratio 0.39), and the blood pressure had fallen to 150/90. An electrocardiogram taken shortly after admission revealed an inverted T-wave in Lead I (Fig. 2), and subsequent curves which were obtained at irregular intervals also showed T-wave changes. It is significant that the T-wave abnormality which was originally present in both Leads I and II disappeared as the patient's condition improved. During the first ten days in the hospital several new hemorrhages appeared in the eyegrounds.

On Oct. 7, 1935 (the fifth hospital day), a biopsy of deltoid muscle revealed a subacute perivascular inflammation involving particularly the arterioles (Fig. 3). Another biopsy, Nov. 11, 1935, showed that the perivascular process was less severe and of a more chronic nature. A third biopsy was done Feb. 20, 1936 (Fig. 4). At

this time, five months after the acute illness, there was very slight thickening of the intima, but the inflammatory process had disappeared entirely.

CASE 2.—The patient was a white girl, 12 years of age, who was admitted to the University Hospital Feb. 3, 1937, complaining of swelling of the face and ankles, loss of appetite, and weakness. The past history was irrelevant except for the fact

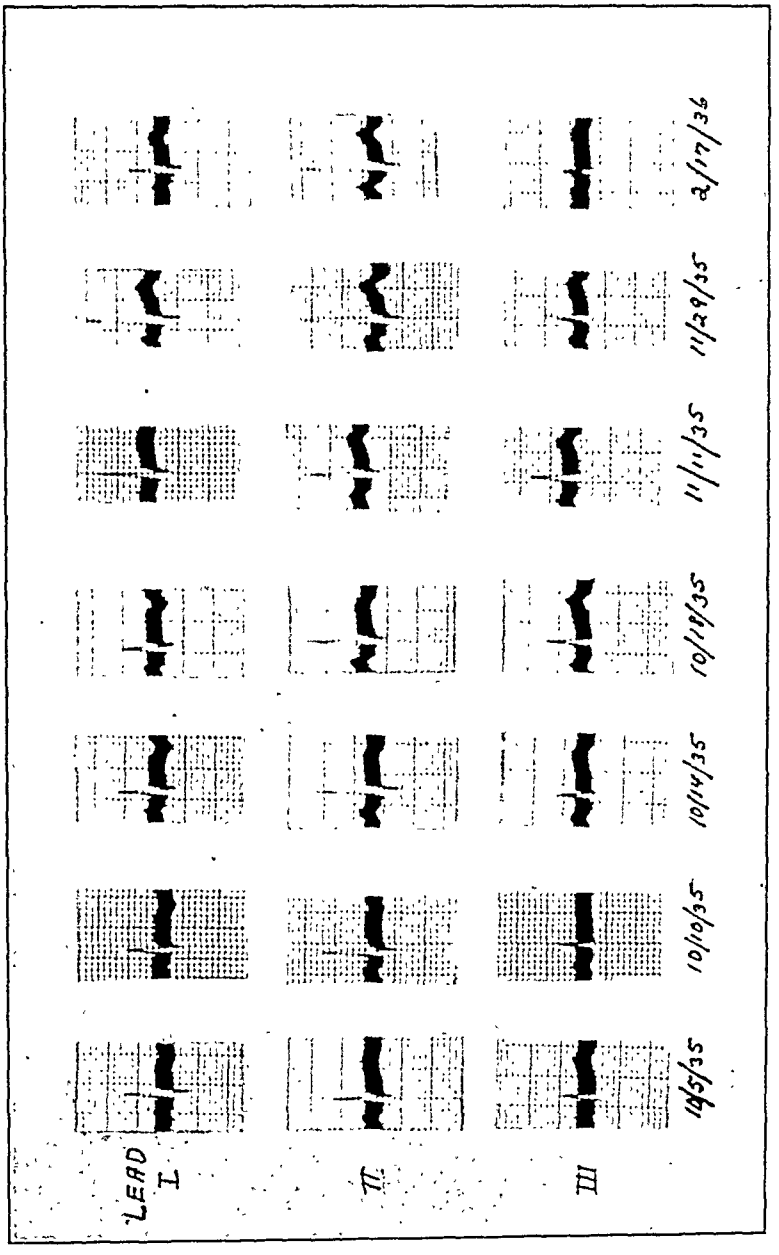

Fig. 2.

that she had had diphtheria when she was six years old. Severe epistaxis occurred at this time, but the child recovered and remained well until Christmas, 1936. At that time she contracted a cold and sore throat, followed in a few days by generalized aches and pains, dizziness, nausea, and vomiting. After one week of rest in bed she returned to school but had no appetite and complained of dizziness. One month before she came to the hospital, her hands, face, and feet began to swell. Two days before admission she had epistaxis and also expectorated some blood, and albumin and blood were found in her urine.

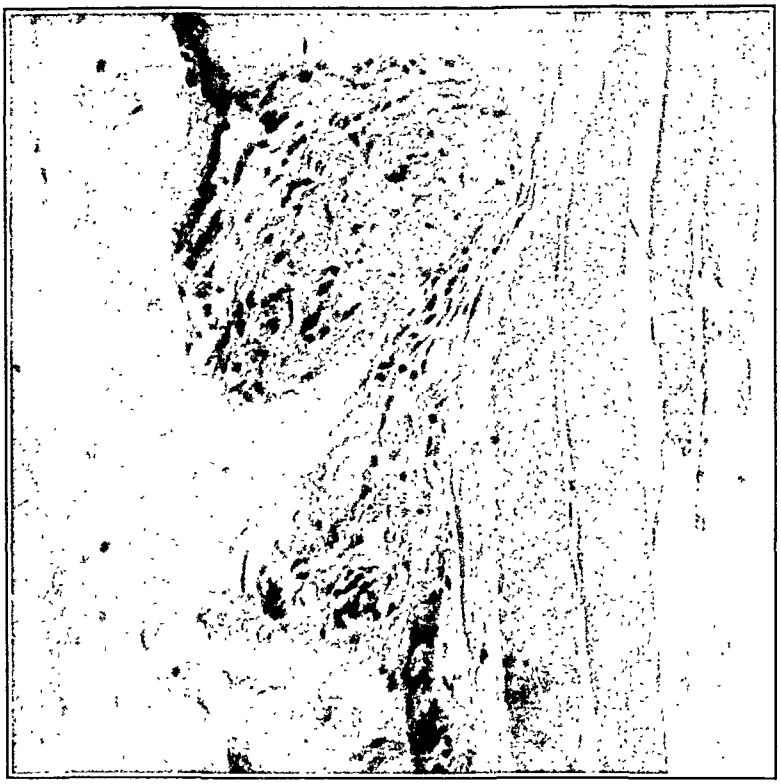

Fig. 3.

Fig. 4.

The child was quite ill and listless. Her skin was very pale. The face was puffy, and there was edema of the lower extremities. Several ecchymoses were present over the feet and ankles. The eyegrounds were normal. The pharynx was reddened and the tonsils and adenoids were greatly enlarged. Several cervical lymph nodes were palpable. A few râles were heard at the base of the left lung. The heart was definitely enlarged, with the left border at the anterior axillary line. A systolic murmur was heard at the apex and at the pulmonic area, and the pulmonic second sound was accentuated. The blood pressure was 110/65. There was tenderness over both kidneys.

The urine contained albumin (graded ++++) and blood (graded ++++, Meyer's test); its specific gravity was 1.010. The erythrocyte count was 3,000,000, the

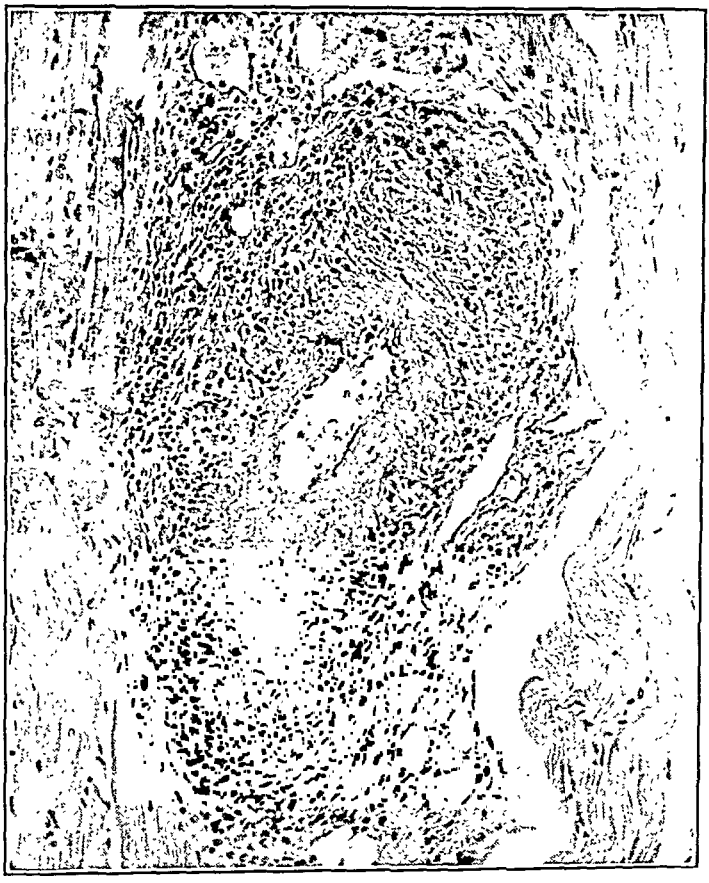

Fig. 5.

leucocyte count 22,500, and the hemoglobin 70 per cent (Sahli). Chemical examination of the blood revealed the following: nonprotein nitrogen, 96 mg. per cent; calcium, 7.8 mg. per cent; phosphorus, 4.8 mg. per cent; total serum protein, 6.1 per cent (albumin 2.3, globulin 3.3, fibrinogen 0.5). The total amount of protein in the urine for a twenty-four-hour period was 12 gm. A blood culture remained sterile.

The rectal temperature varied from 100 to 104° F. throughout the period of observation. The patient became increasingly edematous, and the urine consistently contained large amounts of albumin and blood.

On the third hospital day gallop rhythm and pulsus alternans were discovered. A teleoroentgenogram confirmed the clinical impression that the heart was enlarged. On the seventh hospital day the blood pressure was 135/90, on the thirteenth day 300/100, and on the seventeenth day 190/80. The patient died eighteen days after admission.

Post-mortem examination revealed acute arteriolitis involving some of the vessels in practically all of the tissues of the body (skeletal muscle, brain, heart, kidneys, alimentary tract, pancreas, liver, adrenals, urinary bladder, genitals); acute glomerulonephritis; generalized edema; left ventricular hypertrophy; and necrotizing lobular pneumonia. A specimen of blood taken post mortem contained 196 mg. per cent of urea nitrogen and 9.1 mg. per cent of creatinine.

The lesion seen in a section taken from the pectoralis major is typical (Fig. 5). In many of the arterioles and smaller arteries the muscle layer was the seat of marked hyaline necrosis, and an inflammatory process, with lymphocytes, large mononuclear cells, and many polymorphonuclear leucocytes, was spreading toward the lumen. There were many areas of replacement fibrosis of the vessel wall, and

Fig. 6.

frequently the lumen was almost obliterated. The stage and degree of change within the arterioles were variable; some appeared normal, in others there was evidence of an acute process, and in still others the fibrosis and slight leucocytic infiltration were indicative of an old lesion in the stage of healing. No aneurysms or thrombi were seen. The striated muscle showed scattered areas of degeneration which were doubtless the result of the vascular lesions.

The heart weighed 260 gm. The wall of the left ventricle was 1.6 cm. thick, whereas that of the right measured only 4 to 6 mm. The coronary arteries were collapsed, but patent. No areas of scarring were found in the myocardium; the muscle was firm and pale. The valves were normal. Of four sections taken from the myocardium, three showed only slight vascular disease, but in the fourth it was severe (Fig. 6). The walls of several coronary arteries were greatly thickened, their lumina were decreased in caliber, and the muscle layer had been replaced by fibrous

tissue and infiltrated with leucocytes, including a few eosinophiles. The small vessels within the myocardium were similarly altered, but only one showed the acute stage of arteritis seen in the arterioles of the pectoral muscle.

SUMMARY

Both of these patients presented the clinical manifestations of acute nephritis with cardiac failure. The second patient had a widespread inflammatory lesion of the arterioles, including those of the heart, but the glomerular damage was minimal. Judging from the arteriolar changes in the straited muscle, the hemorrhages in the ocular fundi, the hematuria, hypertension, and cardiac failure, it is probable that the first patient had the same disease as the second. We believe that the histologic evidence of widespread vascular disease in these two patients warrants consideration of the following two possibilities: (1) that acute nephritis is part of a widespread vascular disease which is occasionally severe enough to be called panarteriolitis, or (2) that many patients who seem to have acute nephritis with cardiac failure actually have panarteriolitis with involvement of the vessels of the myocardium.

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A NEW SENSITIVE RECORDING OSCILLOMETER*

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THE potential usefulness of oscillometry in the investigation of peripheral vascular phenomena is only partially realized with the oscillometers now in use. These instruments are so insensitive as to permit measurements only in those parts of the extremities which are traversed by arteries of considerable size, and the measurements so obtained reflect chiefly the condition of these relatively large vessels. It is well known, however, that circulation through the small vessels of the arterial system, as estimated from the appearance and functional capacity of an extremity, may be surprisingly efficient in spite of strikingly diminished oscillometric readings. Conversely, the patency of the peripheral arterioles may be greatly reduced without a corresponding decrease in oscillometric measurements as they are usually made. This is a common observation during the spasms of Raynaud's disease. It is clear that the data obtainable from the leg or arm are inadequate for estimating the status of the digits.

The purpose of the present communication is to describe a new type of oscillometer suitable for making precise measurements directly upon the toes and finger tips. The oscillations recorded in these locations necessarily reflect the pulsation of small vessels, since no large vessels are found there, and for this reason the magnitude of oscillation is greatly influenced by the state of peripheral vascular tonus. It is probable also that local blood pressure may be estimated from the tracings in a manner analogous to the familiar use of the ordinary oscillometer for this purpose, but this has not been checked by direct intravascular pressure measurements. Similarly, the instrument may be used to measure the blood pressure of small laboratory animals.

The oscillometer is shown in Fig. 1, and its construction is indicated schematically in Fig. 2. Vascular pulsations are transmitted from the cuff *A* to the membrane *B* through an incompressible fluid medium (alcohol), in which a distensible tambour *C* is interposed. This tambour permits the cuff pressure to be varied at will by means of the compression bulb *D* and tank *E* while the mean pressure at the membrane is maintained at zero with the leveling cylinder *F*. In each instance the connection to the pressure-regulating device is made through a long length of coiled metal tubing *G*, *H*, in order to increase the inertia of these parts of the fluid system. The membrane *B* is in close proximity to a vent *J*, through which compressed air flows under constant pressure. Movements of the membrane alter the clearance at the

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vent and so regulate the escape of air through it. The resulting fluctuations of pressure within the chamber *K* are recorded by the tambour *L*. The mean cuff pressure is recorded by the tambour *M*, and in order to permit the use of two cuffs an outlet *N* is provided for connection of the proximal cuff *O*. By these means the vascular pulsations actuate the membrane *B*, which in turn regulates the pressure in the chamber *K* and so produces enormously amplified oscillations of the recording tambour *L*. Since *L* operates under a relatively high pressure there is ample power to operate the recording mechanism. The oscillations may be still further amplified by connecting, in place of the tambour *L*, another diaphragm *P* whose movements regulate the escape of air from a second vent *Q*. This vent is then connected to the recording tambour *L*. The change from first to second stages of amplification is effected by means of the valves *R* and *S*.

The cuff *A* is made of reinforced latex rubber, thin and yielding at its inner surface and sides, but relatively inelastic at its outer surface. It is 3 cm. wide and 10 cm. long with a natural curvature adapting it to the digit. In order to minimize

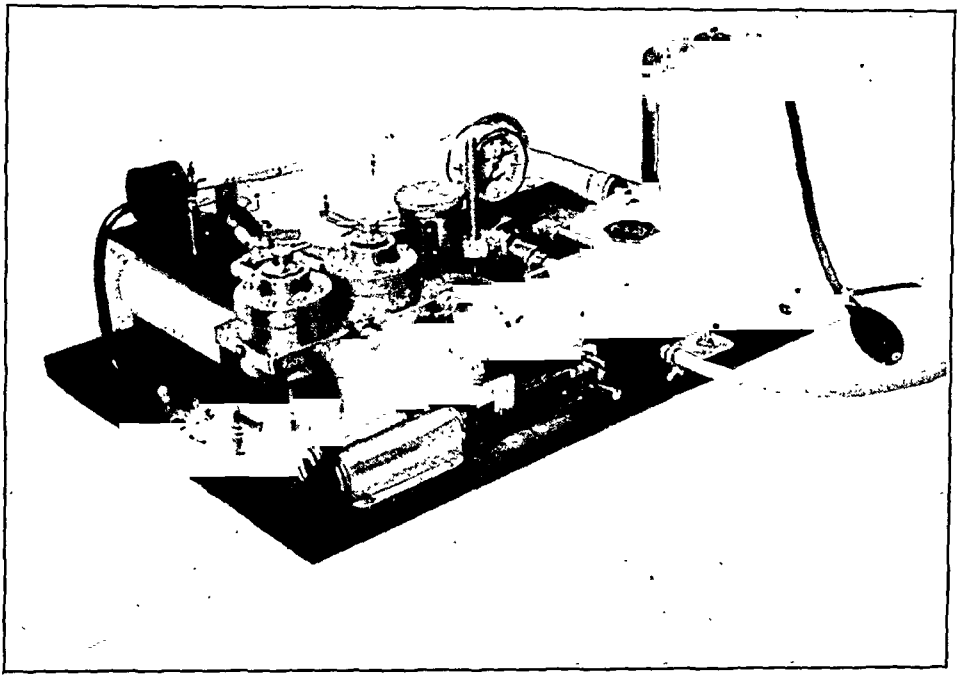

Fig. 1.—The new oscillometer.

damping of vascular pulsations, the cuff is connected to the amplifier through a relatively rigid short rubber tube. The cuff should be at the same level as the fluid in tank *E* in order to avoid a hydrostatic error in recording the mean cuff pressure. Tambour *C* is fashioned from a metal sylphon bellows 1⅝ inches in diameter.* Membrane *B* is 1.25 cm. in diameter, is made of thin rubber dam and is under very little tension. A thin metal disk three-quarters the diameter of the membrane is cemented to the central portion of its upper surface. This furnishes a smooth flat contact surface for the vent.

It is apparent that for maximum sensitivity of the machine, the transmission of pulsatile forces through the tubes *H* and *G* must be effectively damped. If the tubes are too short they do not introduce sufficient inertia to accomplish this result. On the other hand, excessively long tubes produce an undesirable lag in reaching a pressure equilibrium. As a compromise, *H* is about 2 meters long and *G* slightly longer, ⅛ inch copper tubing being used for both. A more perfect but less con-

*Manufactured by the Fulton Sylphon Company.

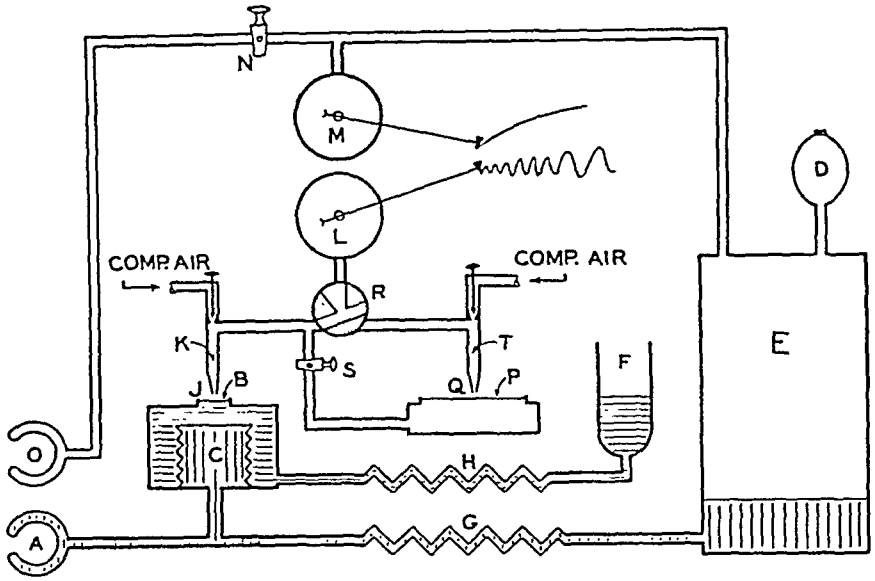

Fig. 2.—Schematic drawing of oscillometer.

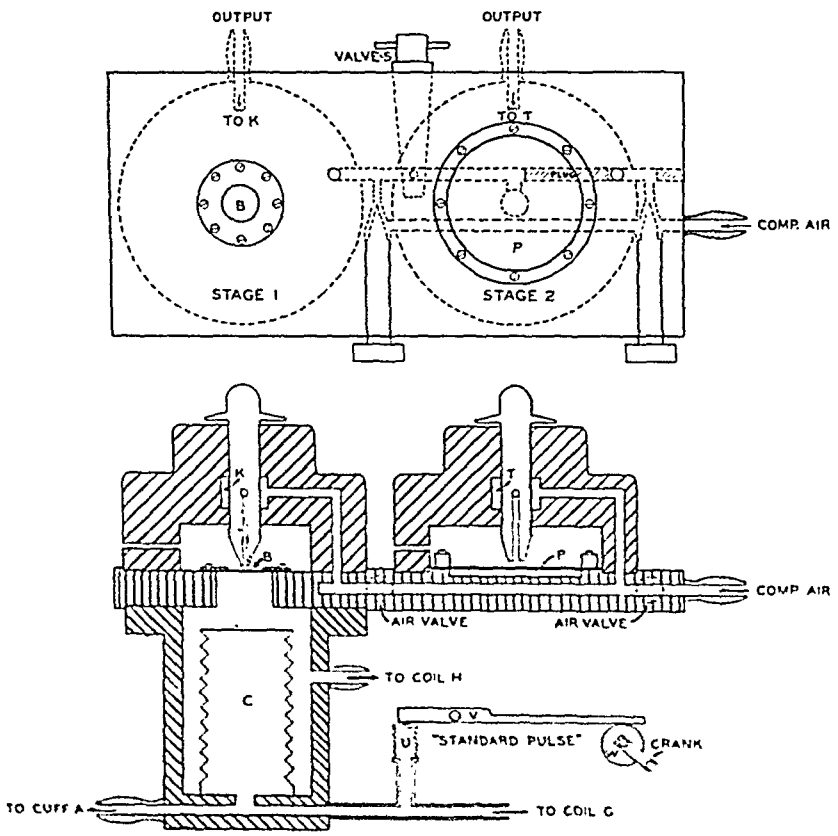

Fig. 3.—The "standard pulse" and two-stage amplifying unit.

venient arrangement utilizes very long tubes with by-pass valves to be opened while the mean cuff pressure is changed. The cylinder *F* is 5 cm. wide, so that the level of fluid within it changes but little as a result of changes in the distention of tambour *C*. A finely threaded, calibrated screw regulates the clearance of vent *J*, whose aperture at the tip is 0.1 cm. in diameter. The tambour *L* is a modified Tycos sphygmomanometer. A rod is soldered to the large gear within and projects through a slot cut in the side of the case. Hinged to this rod is a long, metal, capillary-tube pen which dips into an inkwell mounted above the gear. The pen swings in a horizontal plane over the table of a motor-driven paper-feeding device. The tambour operates at a mean pressure of about 170 mm. of mercury. Tambour *M* is a pressure meter of 0 to 500 mm. of mercury range.*

Compressed air which furnishes the power for driving the recording tambour *L* is first passed through a filter and Hoke "Pheonix" pressure regulating valve, which are not indicated on the diagram. The rate of air flow into the chambers *K* and *T* is regulated by calibrated needle valves. In order to be sure that the rate of inflow will be relatively little influenced by the pressure changes occurring within the chambers during the operation of the oscillometer, a line pressure of 30 pounds per square inch is employed. The membrane *P* is 4.2 cm. in diameter and is made of latex rubber, 0.2 cm. thick, in which is imbedded a metal disk (1.8 cm. in diameter) to keep the central portion flat. Another small thin disk is cemented to its upper surface for contact with the vent *Q*, whose aperture is 0.225 cm. in diameter at the tip. The liquid in the fluid system communicating with the cuff *A* is 70 per cent alcohol, which was selected because of its low viscosity and specific gravity. Water is used in the remainder of the fluid system because of the destructive action of alcohol upon the membrane *B*.

The selection of a practical unit for expressing oscillometric measurements depends upon the characteristics of the instrument employed. Units of volume or of pressure are both unsuitable since the operation of the oscillometer is neither isobaric nor isometric, but involves simultaneous changes in both pressure and volume, and hence measures a composite effect. Moreover, in the instrument here described, the magnitude of oscillation is somewhat dependent upon the pulse rate and also upon minor changes in the adjustment of the apparatus, which may slightly alter its sensitivity. For these reasons the instrument is calibrated in terms of a reproducible arbitrary unit, or "standard pulse." This device produces impulses of uniform magnitude and may be operated at the same rate as the pulse, thus automatically correcting for this variant. In practice the standard pulse is always so operated at the end of a determination, and the magnitude of vascular oscillations may then be expressed in terms of the standard, which facilitates comparison with other determinations.

The standard pulse machine, represented in Fig. 3, consists essentially of a small metal tambour *U* intermittently compressed by means of a lever *V* and slightly eccentric cam *W* so as to displace 0.005 c.c. with each stroke. In the same figure the two-stage amplifying unit is illustrated in detail to indicate the relationship of the various parts.

The sensitivity of the oscillometer and the appearance of records made with it are illustrated by Fig. 4, 5, and 6. Fig. 4 is the oscillogram of the distal phalanx of the index finger of a normal subject, made with the single-cuff technique and one stage of amplification. The tracing is read from right to left, and the falling line indicates the mean cuff

*Manufactured by the Bristol Company.

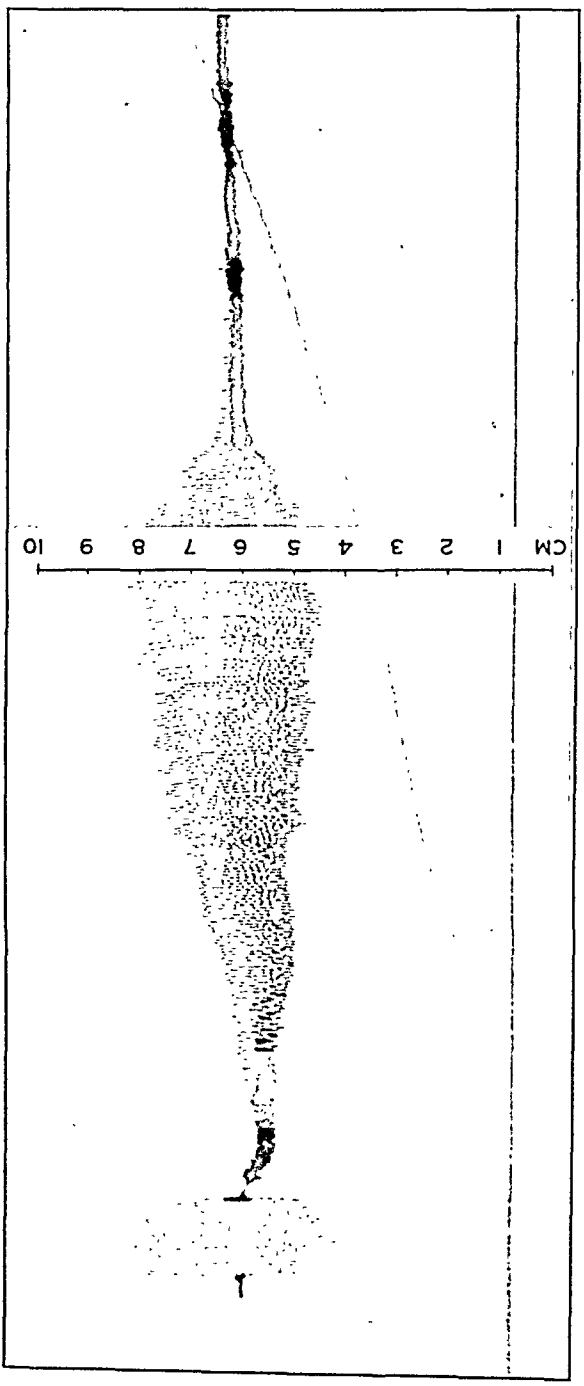

Fig. 4.—Oscillogram of a normal finger tip, first stage.

pressure. The small oscillations of approximately equal size at the extreme right are supramaximal. The tracing at the extreme left is the standard pulse curve. It may be seen that the largest vascular pulsation

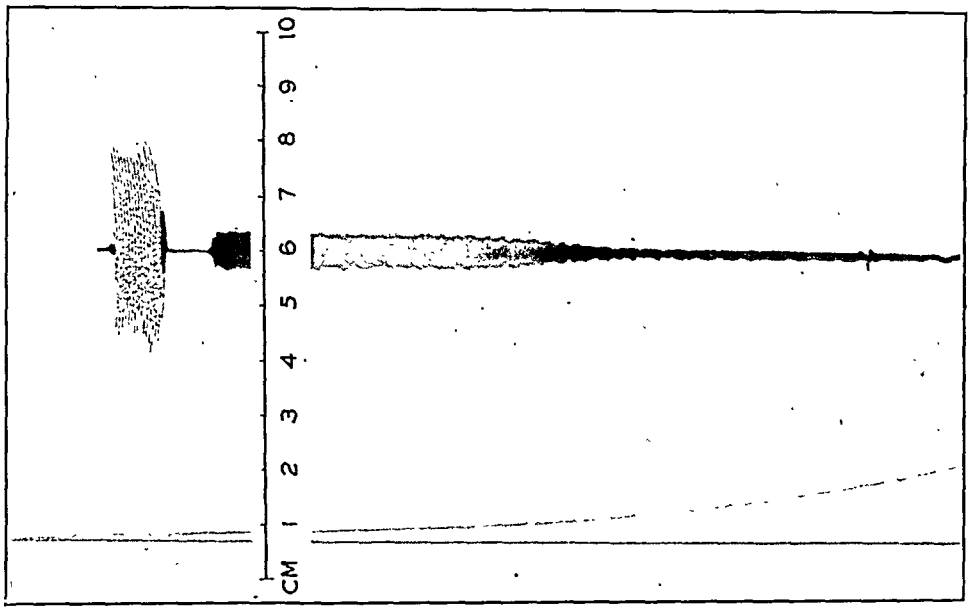

Fig. 5.—First stage oscillogram of a toe, in a patient with arteriosclerotic peripheral vascular disease.

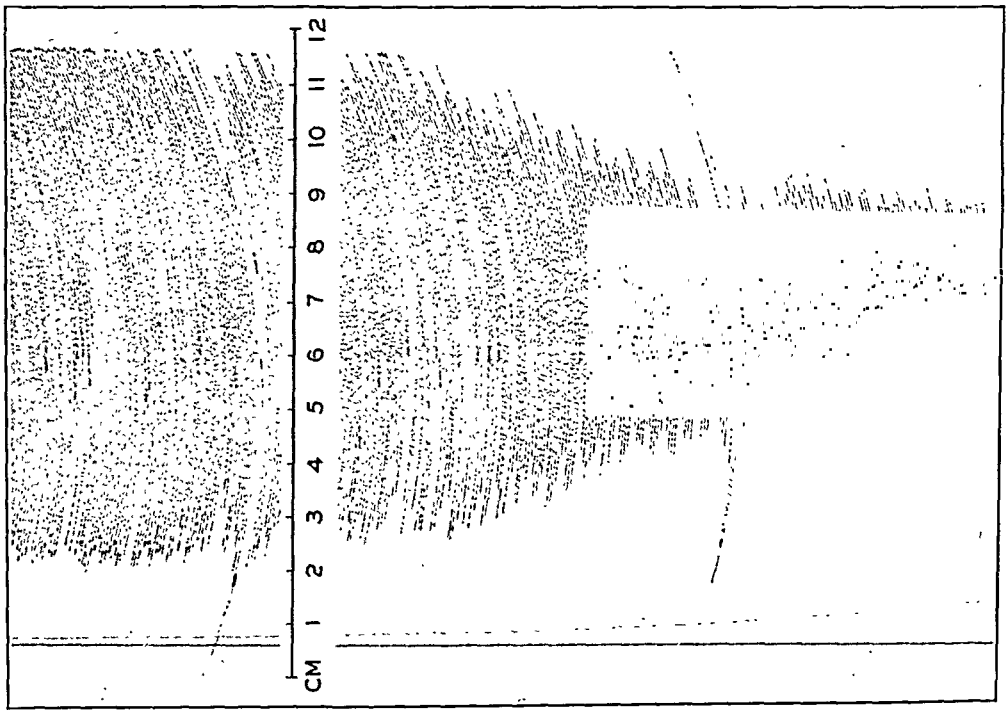

Fig. 6.—Second stage oscillogram of the same toe as that from which Fig. 5 was obtained.

is 3.7 cm. long, or approximately 0.9 standard pulse units. Using the criteria generally employed for estimation of blood pressure from oscillometric measurements, the local blood pressure in this instance is

115/65. The oscillations shown here are of the usual magnitude for a finger tip and are by no means the largest observed. For pulsations of this size the second stage of amplification is not used because the oscillations then greatly exceed the range of the recording tambour.

Fig. 5 is the oscillogram of the great toe of a 54-year-old diabetic patient with arteriosclerotic peripheral vascular disease whose oscillometric indices as measured with the Pachon oscillometer were 2.0 at the thigh, 0.5 below the knee, and 0.1 at the ankle. The tracing in Fig. 5 was made with one stage of amplification at a room temperature of 75° F., and the mean cuff pressure and standard pulse curves are shown as in the preceding figure. The oscillometric index is 0.2 standard pulse units and the local blood pressure is notably low. Immediately after making the record shown in Fig. 5 another oscillogram was made on the same subject, using the second stage of amplification under conditions otherwise identical. A portion of this record is shown in Fig. 6. The largest oscillations represent a full scale deflection of the instrument.

The instrument may be used for measuring blood pressure in dogs and rabbits. Rarely, with a suitable cuff, vascular pulsations may be detected in the rat's tail, but the tracing is generally obscured by respiratory and other extraneous movements.

SUMMARY

A sensitive recording oscillometer suitable for precise measurement of the vascular pulsations in the toes and finger tips of man is described. The instrument is also useful for measuring blood pressure in the limbs of small laboratory animals. The use of a standard pulse eliminates errors inherent in the instrument and permits the pulsations to be expressed in terms of the standard pulse.

Department of Clinical Reports

AURICULOVENTRICULAR DISSOCIATION FOLLOWING SCARLET FEVER*

Report of a Case

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AURICULOVENTRICULAR dissociation as a sequela of scarlet fever has hitherto not been recorded so far as I can determine. Shookoff and Toran,[1] in 1931, could not demonstrate a prolongation of the P-R interval in an electrocardiographic study of a series of scarlet fever patients. On the other hand, Wichstrom,[2] in 1933, observed prolongation of the auriculoventricular conduction time beyond 0.2 sec. in five of a group of 100 scarlet fever patients. Berger and Olloz,[3] in 1934, studied sixty-six scarlet fever patients clinically and electrocardiographically and observed electrocardiographic evidence of myocarditis in four of these, but no evidence of complete heart block. The studies of Faulkner, Place, and Ohler[4] on 171 scarlet fever patients revealed abnormal electrocardiograms in eleven individuals, an incidence of 6 per cent. In five patients the abnormalities consisted merely of prolongation of the P-R interval beyond 0.2 sec. Seventy-five per cent of the patients who developed abnormal electrocardiograms were between four and sixteen years of age. The severity of the illness had no influence on the degree of electrocardiographic changes. None of the abnormalities was observed prior to the thirteenth day; the majority of the abnormal records were grouped between the nineteenth and thirty-fourth days.

The likelihood of pathologic involvement of the heart, including the conduction system, in patients with scarlet fever is emphasized by Brody and Smith,[5] who found lesions of varying severity in over 90 per cent of the cases which they studied.

CASE REPORT

R. N., a boy 18 years of age, entered the Jewish Hospital June 10, 1936, because of precordial distress, dizziness, and occasional unconsciousness.

The past medical history was negative except for measles, mumps, chicken pox, grippe, and tonsillitis.

The present illness dated back to April 4, 1935, when the patient was admitted to the Philadelphia Hospital for Contagious Diseases on the fourth day of an

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attack of scarlet fever. At that time his temperature was 102° F. The pulse rate was 108, and the respiratory rate, 24 per minute. The scarlet fever was of average severity. Examination of the patient's heart was reported as showing nothing abnormal aside from the accelerated rate. On April 5 the patient's pulse rate was 116, on April 7, 74; and April 9, 72 beats per minute, and the temperature was normal on the latter date.

On April 18, the eighteenth day of the illness, the pulse rate was reported as 50 per minute and then fluctuated from 50 to 60 per minute until the twenty-third day of the disease, when it rose to 80 per minute. On April 29, 1935, a systolic murmur was audible at the apex of the heart. On May 2, 1935, the patient was discharged from the Philadelphia Hospital for Contagious Diseases, the final note[6]

Fig. 1.—Patient in stage of decompensation. Marked cyanosis.

stating that there were no abnormal cardiac findings, and that the heart rate was averaging 70 per minute. Electrocardiographic studies were not made during the foregoing period.

Fatigue was an annoying symptom during the subsequent months, and, although the patient returned to school in the fall of 1935, he never felt quite well.

In January, 1936, he had several attacks of dizziness, blurred vision, and dyspnea. In one of the attacks he was quite alarmed about severe precordial distress. On March 25, 1936, and again on May 23, 1936, similar attacks occurred, and, in addition, were accompanied by brief periods of unconsciousness (Adams-Stokes syndrome).

On admission to the hospital June 10, 1936, the patient was fairly well nourished, dyspneic, and cyanotic. The jugular veins were engorged. The size of the heart was within normal limits. A diffuse cardiac impulse was visible in the 3rd, 4th and

5th left intercostal spaces. On auscultation the heart sounds were impaired. The blood pressure was 110/70. Otherwise the examination was negative.

On July 10, one month after admission to the hospital, the patient, while in bed, had a syncopal attack during which he became cold and cyanotic. His cardiac

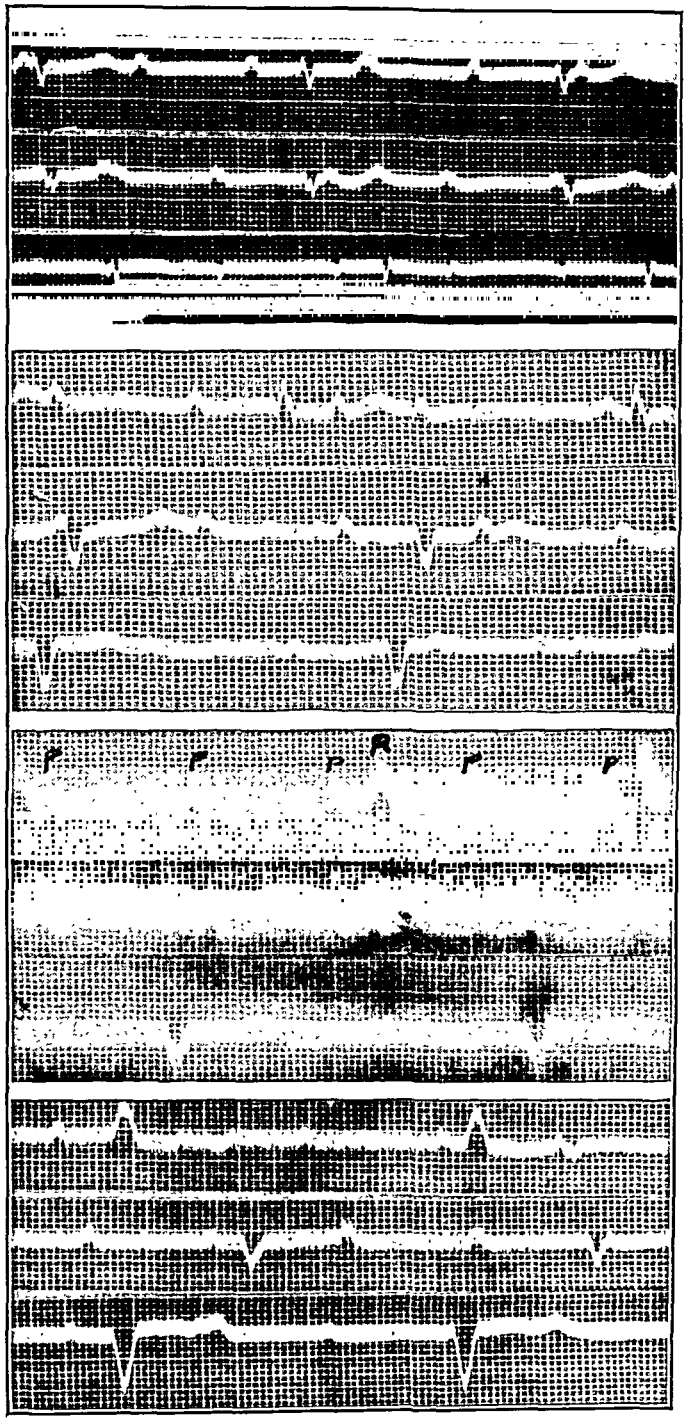

Fig. 2.—*A*, electrocardiogram taken Aug. 7, 1936. Auricular rate, 72; ventricular rate, 32. Complete A-V dissociation.

B, record taken June 11, 1937. Auricular rate, 83; ventricular rate, 33. Complete A-V dissociation.

C, Electrocardiogram made Jan. 12, 1938. Auricular rate, 72; ventricular rate, 28-30. Complete A-V dissociation. Arborization block.

D, Record taken May 5, 1938. Auricular rate, 83; ventricular rate, 30. Complete A-V dissociation. Left bundle branch block. Severe myocardial disease.

rate was noted to be 40 per minute. Electrocardiographic study on July 11 indicated complete heart block with an auricular rate of 107 and ventricular rate of 41 per minute.

Cardiac decompensation followed and has persisted despite the use of all known therapeutic measures. The cyanosis (Fig. 1) has always been marked and jugular pulsation can be noted frequently. Cardiac hypertrophy developed slowly.

On auscultation one can frequently hear the auricular sounds over the 3rd and 4th left interspaces, in addition to the changing quality and intensity of the first cardiac sound. The cardiac rate ranges from 28 to 40 per minute. The systolic blood pressure varies between 90 and 100 mm. Hg and the diastolic, between 60 and 75. Repeated electrocardiograms during 1936-1937-1938, several of which are shown in Fig. 2, all indicated severe myocardial damage and complete heart block.

Paracentesis thoracis has been necessary eleven times since Sept. 8, 1936, with removal of a total of 9825 c.c. of clear fluid; abdominal paracentesis has been performed on thirteen occasions since Oct. 31, 1936, with removal of a total of 48,012 c.c. of clear fluid; and venesection has been necessary on five occasions since Sept. 24, 1936, with removal of a total of 925 c.c. of blood.

On Jan. 20, 1938, the circulation time from arm to tongue was 42 seconds, and the ether time was 22 seconds. The venous pressure was difficult to measure.

Various other laboratory data were all essentially negative.

COMMENT

The clinical history herein presented indicates that the patient did not evidence any cardiac involvement prior to April 4, 1935, when he was admitted to the Philadelphia Hospital for Contagious Diseases during an attack of scarlet fever. Observation during the patient's stay at this hospital disclosed a bradycardia which occurred on the eighteenth day of the disease, the cardiac rate being recorded at 50 per minute and then varying from 50 to 60 per minute for five days. Later the pulse rate increased to 80 per minute, but, when the patient was discharged from the Philadelphia Hospital for Contagious Diseases, the rate was 70 per minute. The slowing of the cardiac rate to 50 per minute during the attack of scarlet fever suggests that scarlet fever was the cause of the bradycardia.

Faulkner and his co-workers[4] observed that in scarlet fever the majority of cardiac abnormalities were noted after the thirteenth day and that most of the abnormal electrocardiographic records were grouped between the eighteenth and thirty-fourth days. This patient evidenced the slow heart rate on the eighteenth day of his attack of scarlet fever.

CONCLUSION

A case of complete auriculoventricular dissociation as a sequel of scarlet fever emphasizes the importance of careful follow-up electrocardiographic studies of all individuals convalescing from the disease. Such investigations would in all probability reveal additional instances of auriculoventricular dissociation. If this proves to be the case, it would seem logical to conclude that a longer rest period for patients

recovering from scarlet fever should be prescribed. This patient, who is still under observation, has complete heart block and cardiac decompensation.

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PAROXYSMAL BUNDLE BRANCH BLOCK ASSOCIATED WITH PHYSIOLOGIC CHANGES IN A PATIENT WITH ORGANIC HEART DISEASE

Report of Case*

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RECENTLY, Comeau, Hamilton, and White[1] reported thirteen cases of paroxysmal bundle branch block associated with heart disease and collected 58 additional cases from the literature. They excluded the cases described by Wolff, Parkinson and White,[2] in which there were wide QRS complexes, short P-R intervals, and no evidence of organic heart disease. At about the same time Bishop[3] described a case of transient, recurrent bundle branch block in a patient with organic heart disease. The following is a report of an additional case.

CASE REPORT

History.—A white woman, 66 years old, was seen March 26, 1938. She complained of paroxysmal nocturnal dyspnea, orthopnea, and dyspnea on exertion, all of three months' duration. Three years previously she had begun having severe frontal and parietal headaches accompanied by visual disturbances, tinnitus, vertigo, and syncope. One year later she had a cerebral hemorrhage and left-sided hemiplegia from which she recovered in three months. There had been no edema of the ankles. The past and family histories were irrelevant.

Physical Examination.—The patient was acutely ill and markedly orthopneic. Examination of the eyegrounds showed moderate tortuosity of the retinal arteries. The jugular veins were distended with the patient in a semiupright position. The respiratory rate was increased. The percussion note was dull below the angles of the scapulae. The breath sounds were diminished in intensity at both bases and accompanied by numerous, medium, moist râles. The radial pulses were of poor quality, equal and, except for an occasional extrasystole, regular. The pulse and heart rates were 118 per minute, the blood pressure 220/160. Precordial activity was increased. The point of maximum impulse was seen and felt as a diffuse pulsation in the fifth interspace in the left anterior axillary line. The area of cardiac dullness was enlarged markedly to the right and left. The heart sounds were of poor quality, and there were no accentuations. Except for an occasional extrasystole the beating was regular. A soft untransmitted systolic murmur was present at the apex. The edge of the liver was palpable just below the costal margin and was tender. There was no ascites nor dependent edema. There was no paralysis, but residual hemiplegic signs were present on the left side.

The specific gravity of the urine was 1.026, and it contained a little albumin (+) and a few granular casts. Examination of the blood showed no significant changes; the blood Wassermann reaction was negative. The sedimentation rate was 0.7 mm. per minute.

*From the Department of Medicine, the South Bend Clinic.
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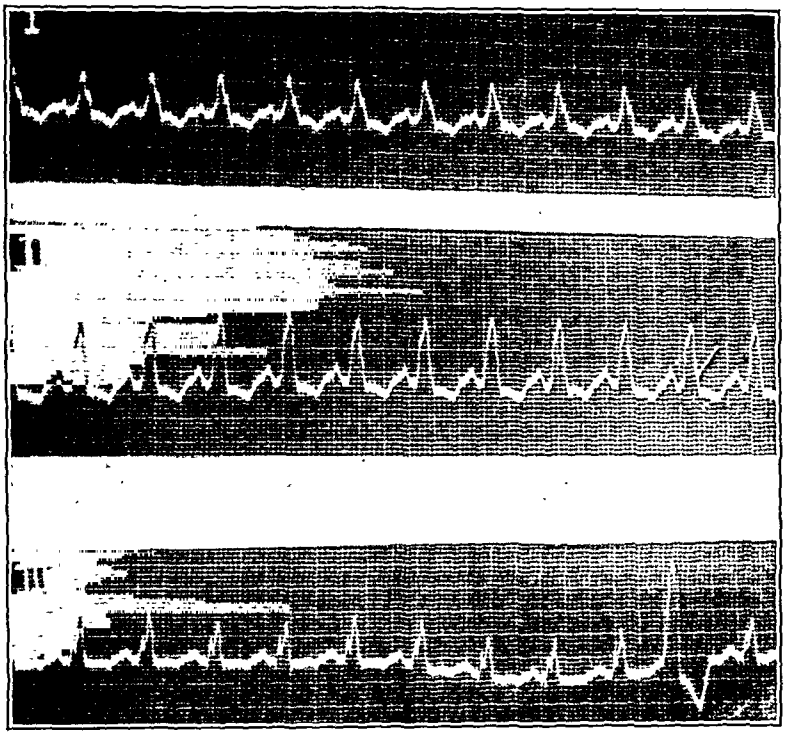

Fig. 1.—Electrocardiogram taken March 26, 1938, while patient had acute heart failure. Auricular and ventricular rates, 115. P-R interval, 0.14 sec. QRS time, 0.12 sec. Time marker, 0.20 sec. and 0.04 sec.

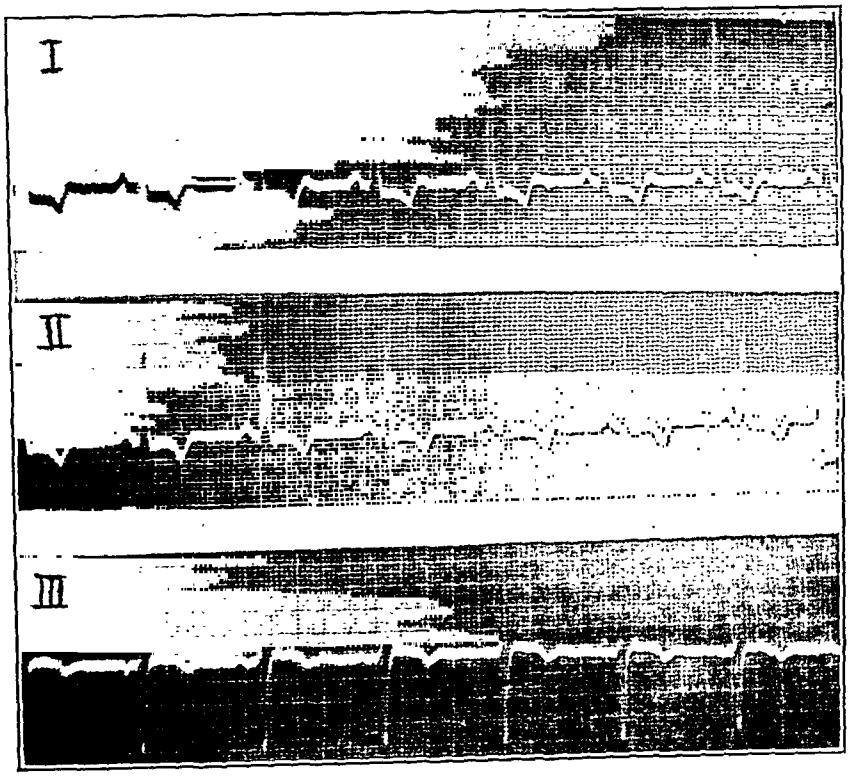

Fig. 2.—Electrocardiogram taken April 4, 1938, nine days after admission. The heart is compensated. Auricular and ventricular rates, 65. P-R interval, 0.16 sec. QRS time, 0.08 sec. Time marker, 0.20 sec. and 0.04 sec.

A teleoroentgenogram showed marked enlargement of the heart to the right and left and extensive passive hyperemia of the lungs.

An electrocardiogram (Fig. 1) showed auricular and ventricular rates of 115, a P-R interval of 0.14 sec. and a left* bundle branch block with QRS time of 0.12 sec. The T-waves were inverted with low points of origin in Leads I and II, and followed the isoelectric line in Lead III.

The diagnosis was hypertensive heart disease with cardiac enlargement and congestive failure, coronary sclerosis, left bundle branch block, and questionable coronary thrombosis.

Course.—The patient was digitalized and given the usual treatment for cardiac failure. She was discharged from the hospital April 4, nine days later, with limited cardiac reserve but no evidence of decompensation. The heart rate was 68 and the

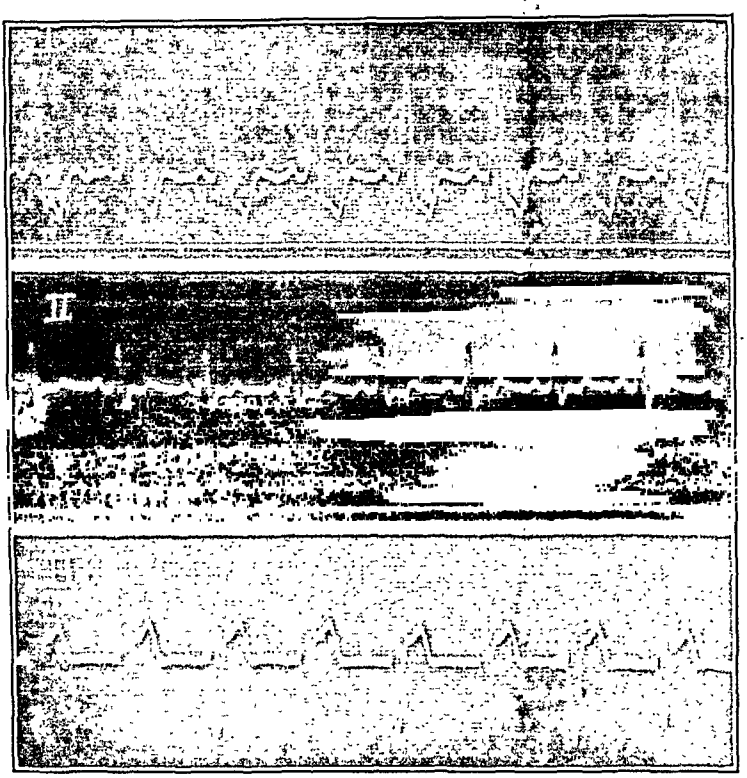

Fig. 3.—Electrocardiogram taken May 31, 1938, eight weeks after discharge. The heart is compensated. Auricular and ventricular rates, 75. P-R interval, 0.18 sec. QRS time, 0.13 sec. Time marker, 0.20 sec. and 0.04 sec.

blood pressure 208/140. The point of maximum impulse was forceful and well localized. Lateral to it was a systolic retraction. The area of cardiac dullness had diminished and the heart sounds had improved in quality. The systolic murmur at the apex had increased in intensity but was soft in quality.

An electrocardiogram (Fig. 2) taken at this time indicated that the bundle branch block had disappeared. The auricular and ventricular rates were 65, left axis deviation was present, and the voltage was high.

The patient resumed her usual activities with some restrictions and returned, May 31, eight weeks later, for re-examination. The heart was well compensated, the rate 76 and the blood pressure 224/138. An electrocardiogram (Fig. 3) indicated

*The designation of left bundle branch block accords with the terminology proposed by Wilson and his co-workers.[4]

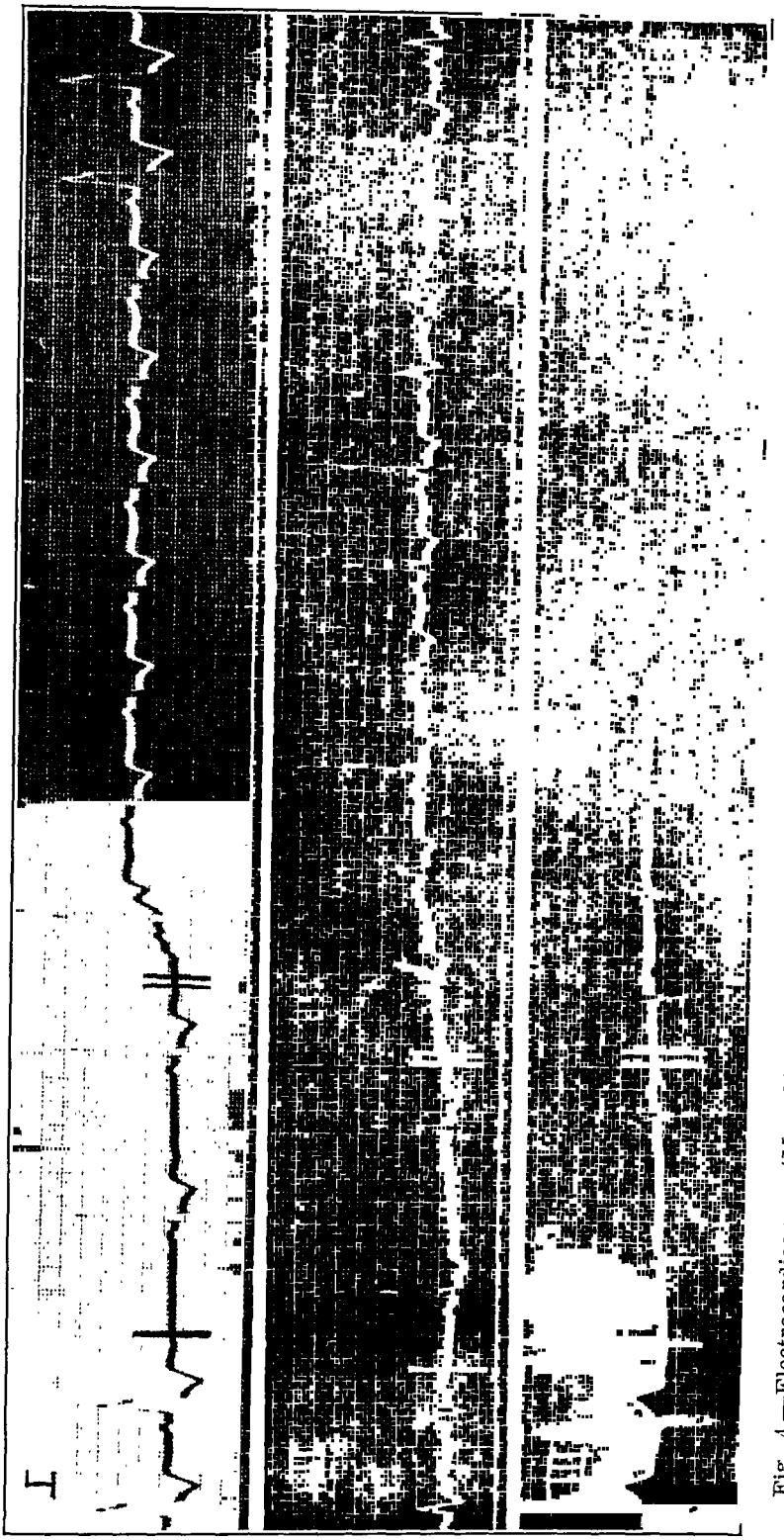

Fig. 4.—Electrocardiogram (May 31, 1938) showing the effect of carotid sinus pressure. The single vertical white line denotes application of carotid sinus pressure and the double vertical white line denotes release of carotid sinus pressure. Time marker, 0.20 sec. and 0.04 sec.

that bundle branch block had reappeared, and that the auricular and ventricular rates were 75. Fig. 4 shows the effect of carotid sinus pressure. Pressure was applied over the right carotid sinus at a time designated on the electrocardiogram by the single vertical white line. A marked slowing of the rate followed, and there was immediate disappearance of the bundle branch block. Pressure was maintained

for a period covering two ventricular contractions and then discontinued. Discontinuance of pressure is designated by the double vertical white line. At this point the heart rate began gradually to increase. Unslurred QRS complexes of normal duration continued in each lead until a certain critical heart rate was reached. This level was approximately 71 beats per minute, and whenever it was exceeded branch block was re-established. The block continued until it was again abolished by carotid sinus pressure. In Lead II of Fig. 4 there was a premature auricular contraction shortly after the re-establishment of branch block. This resulted in a partial

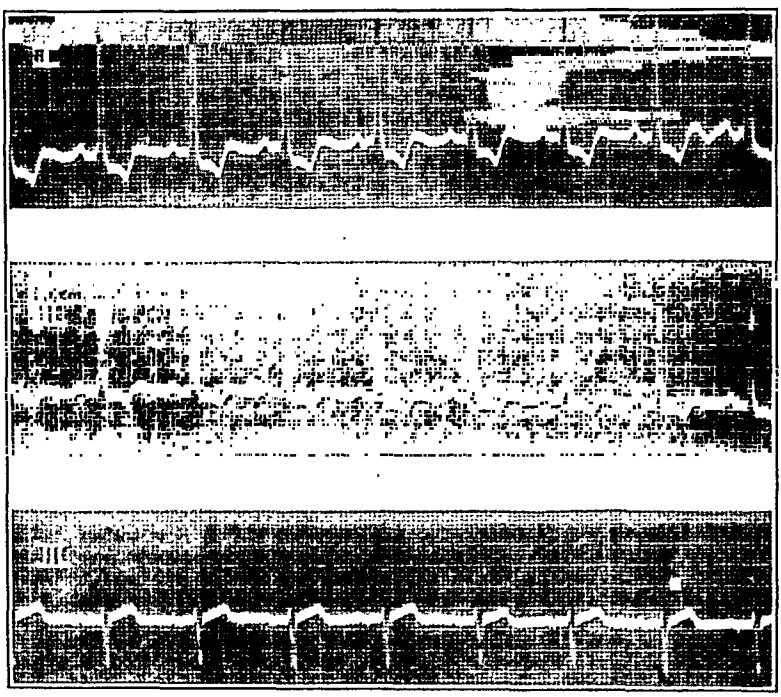

Fig. 5.—Electrocardiogram taken June 14, 1938. Auricular and ventricular rates, 79. P-R interval, 0.22 sec. QRS time, 0.07 sec. Time marker, 0.20 sec. and 0.04 sec.

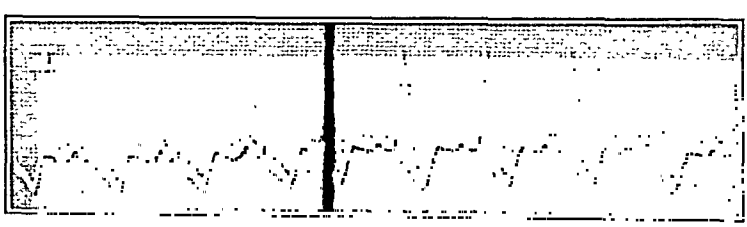

Fig. 6.—Electrocardiogram (June 14, 1938) showing the effect of exercise on intraventricular conduction. The vertical black line divides the records taken before and after exercise. Approximately three minutes elapsed between the end of exercise and the beginning of the second portion of this record. The rate before exercise, 82; three minutes after exercise, 83. P-R interval before exercise, 0.22 sec.; after exercise, 0.20 sec. QRS time before exercise, 0.07 sec.; after exercise, 0.13 sec. Time marker, 0.20 sec. and 0.04 sec.

compensatory pause, and the next QRS complex was not blocked. Those that followed indicated that branch block had been resumed.

On June 14 the patient returned. The pulse and heart rates were 78, and the blood pressure 194/130. There were, otherwise, no significant changes on physical examination.

An electrocardiogram (Fig. 5) taken on this occasion showed no bundle branch block. The QRS time was 0.07 sec., and the auricular and ventricular rates were 79. The patient was given mild exercise which caused marked dyspnea and moderate elevation in heart rate. An electrocardiogram taken immediately after exercise indicated that the rate had increased to 84 and that left bundle branch block had been re-established. After a rest period of twenty minutes a third electrocardiogram showed a rate of 79 with branch block persisting. Right carotid sinus pressure was then applied as formerly. It was followed by a reduction in heart rate and the abolition of bundle branch block. After release of pressure the rate increased gradually to 82, as shown in the first portion of Fig. 6. Bundle branch block, however, was not present. The patient then exercised, causing dyspnea out of proportion to the elevation in heart rate, which increased to 88 as counted from the radial pulse. After a rest period of approximately three minutes, the second portion of Fig. 6 was taken. The rate was now 83, with bundle branch block again present.

DISCUSSION

When this patient first came under observation the bundle branch block was thought to be the result of coronary disease and myocardial fibrosis. The T-wave changes supported this view. Later, with the return of compensation, the block disappeared. Its former presence was then attributed, in part, to anoxemia or nutritional changes in a failing, dilating heart. This explanation, however, would not account for its reappearance within eight weeks, at a time when there was no cardiac failure. Except for a moderate increase in heart rate no significant changes perceptible by physical examination had taken place during this period. The electrocardiogram showed an increase in heart rate from 65 to 75. It was then thought that the increased rate might be an additional or precipitating factor in producing branch block without necessarily invalidating the previous explanations.

Comeau and his co-workers have emphasized this point, and the reader is referred to their article[1] for a comprehensive discussion of the available case material. They call attention to experimental evidence which shows that under certain conditions conduction may be normal at low heart rates and impaired at high heart rates. From their clinical studies they were able to conclude that in some cases the inhibiting factors capable of producing branch block are not effective when the heart rate is below a certain critical level. This critical level may vary in the same individual, but, whenever it is exceeded, branch block ensues. Yater[5] has emphasized the bilateral nature of bundle branch lesions and has demonstrated that the form of the electrocardiogram depends upon which branch is the more seriously damaged. However, metabolic and physiologic factors may be superimposed, and it is not necessary to have complete block anatomically in order to produce the typical electrocardiographic picture. All that is necessary is that the total effect of the inhibiting factors in the one branch be greater than the effect of those along the other branch and in the ventricular myocardium.

In the case under discussion it is difficult to evaluate the exact roles played by the various inhibiting factors in producing branch block. The essential structural factors are myocardial fibrosis and chronic or acute coronary disease, and the physiologic factors deserving consideration are fatigue and recovery time of the conduction fibers, nutrition, oxygenation, and the calcium and potassium metabolism of cardiac tissue. Vagal influences apparently function through the medium of a reduced heart rate, while vasomotor changes do not appear to play a role.

Although the underyling lesion is anatomic in nature, the electrocardiographic picture varies with the physiologic load which the heart is carrying. Under certain conditions a specific relationship exists between the heart rate and the type of intraventricular conduction. In Fig. 4 the release of carotid sinus pressure was followed in each lead by a gradual increase in heart rate until a certain critical threshold was exceeded. Once this threshold was exceeded, branch block ensued. There were no transitional complexes, and the block persisted until again abolished by carotid sinus pressure. The only exception occurred in Lead II of Fig. 4, and served to substantiate the apparent explanation. A premature auricular contraction which produced an incomplete compensatory pause thereby reduced the heart rate sufficiently to permit the appearance of a single unblocked QRS complex. In the succeeding contractions branch block was resumed.

On a subsequent visit the patient had reverted to unblocked intraventricular conduction. Light exercise converted this to blocked conduction which persisted until unblocked conduction was again induced by carotid sinus pressure. On this occasion it was not possible to establish such a close correlation between the heart rate and the type of conduction. Fig. 6 shows both types of conduction at practically the same heart rate. This would seem to indicate that factors other than the heart rate were playing a role in determining the balance between blocked and unblocked conduction. The fact that exercise caused dyspnea out of proportion to the elevation in heart rate is evidence that anoxemia might have been a factor. Conversely, it is known that the inhalation of oxygen[6] will, in certain instances, abolish paroxysmal bundle branch block in organic heart disease.

SUMMARY AND CONCLUSIONS

While it is not possible to draw specific conclusions from the data obtained in this case, certain facts stand out. The essential pathologic changes were hypertensive heart disease with congestive failure and subsequent compensation. In addition, there was electrocardiographic evidence of chronic or acute coronary disease and myocardial fibrosis. Finally, there was throughout the course of the acute illness as well as the convalescence a paroxysmal left bundle branch block which depended on changes in cardiac activity. Most striking of these was the relation-

ship between intraventricular conduction and the heart rate. This relationship, however, was not invariable, and therefore it appears that other physiologic factors, such as anoxemia, were playing a role.

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OBSERVATIONS ON THE MECHANISM OF THE DYING HEART IN A PATIENT WITH VENTRICULAR TACHYCARDIA*

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THESE observations are of unusual interest because they reveal for the first time that with acute coronary thrombosis and ventricular tachycardia the mechanism of the dying heart may be ventricular standstill instead of ventricular fibrillation.

REPORT OF CASE

J. B. G. (Case 51629), a man, aged 52 years, was admitted to the Bayonne Hospital Nov. 24, 1937, and died at 1:45 P.M. on Nov. 25, 1937.

The patient worked as a clerk and was perfectly well until two weeks prior to his admission to the hospital, when he began to complain of uneasiness in the precordial and parasternal regions. One week later he experienced a severe retrosternal pain accompanied by nausea and vomiting and profuse perspiration. Within eighteen hours he was relieved of these symptoms, but he felt too weak to continue work and remained at home. On the evening of Nov. 23, 1937, two days prior to his death, he experienced an attack of breathlessness accompanied by perspiration, anxiety, and precordial distress. He coughed throughout that night, and because of the increasing severity of symptoms he sought hospital care.

Physical examination on admission to the hospital revealed a plethoric, breathless, and orthopneic individual who appeared acutely ill. Large beads of perspiration covered his forehead. His skin was moist, cold, and clammy. His pulse was rapid and feeble. He complained of severe substernal distress, and he felt nauseated. His heart sounds were barely audible at the apex, and his heart rate averaged between 180 and 200 beats per minute. The blood pressure was 84/70. The lungs contained moisture, but the liver and spleen were not palpable.

Morphine was administered in adequate doses and 3 grains of quinidine sulfate were given as soon as the heart rate was found to be accelerated. Because of the increasingly intense cyanosis and breathlessness it was deemed advisable to place him in an oxygen tent, which made him distinctly more comfortable. The quinidine sulfate was continued every hour throughout his stay in the hospital, and the dose was increased to 5 grains when it became apparent that he could tolerate that amount. Fourteen hours after admission his heart rate slowed to 68 beats per minute, but within the next hour ventricular tachycardia returned and persisted until death.

DESCRIPTION OF THE CARDIAC MECHANISM

On Nov. 24, 1937, when his heart rate was discovered to be rapid, the electrocardiogram showed a tachycardia of 187 beats per minute with markedly widened ventricular complexes which were uniform in character from beat to beat (Fig. 1). All of these beats produced audible sounds at the apical region of the heart, as well as palpable pulses. The heart rate was slower on the following day, and, very likely as a result of giving quinidine, the ventricles averaged 150 beats per minute, but no evidence of auricular activity could be made out (Fig. 2). At this time he was semicomatose and began to show signs at the bases posteriorly of consolidation of both lungs. His condition became progressively worse, and on Nov. 25, 1937,

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at 12:40 P.M., when his respirations were 36 per minute and he was in deep coma, he was placed in the electrocardiographic circuit. Tracings were taken intermittently until about twenty-five minutes before death, after which the recording was continuous until all electrical activity ceased.

Ten minutes before his respirations stopped the ventricular rate was variable, averaging 150 beats per minute (Fig. 3), and the ventricular complexes were of lower voltage and wider than the previous ones. When the heart rate increased to 200 beats per minute the voltage of the ventricular complexes was unusually low. In these records evidence of definite auricular activity could well be discerned. Both the auricles and ventricles became slower until the tachycardia was ended by a long postundulatory pause (Fig. 4*A*) of 1 minute and 80 seconds.

In the next few minutes the heart rate averaged 41 beats per minute (Fig. 5*A*). Auricular activity could be made out only rarely, and now the ventricular complexes were wide and bizarre. Shortly the rate increased to 62 beats per minute, but no evidence of auricular activity could be seen (Fig. 6). Thereafter for twenty minutes the rate of the ventricles became progressively slower and the ventricular complexes smaller, until finally, approximately 28 minutes after the patient appeared to be dead, there was complete cessation of electrical activity.

DISCUSSION

There is a general belief based on very meager evidence that ventricular fibrillation is the terminal cardiac mechanism in patients with all forms of ventricular tachycardia,[1] but a search of the literature reveals only a few instances in which ventricular fibrillation was found to be the end-result of ectopic ventricular tachycardia.[2-6] Unfortunately, in none of these reports are there graphic observations of the transition between the ventricular tachycardia and the mechanism of the dying heart. It is very likely that if more records are obtained in such patients just before death, standstill of the heart will be found to be as frequent as, if not more frequent than, ventricular fibrillation.

It is well known from Gaskell's experiments[7] on the hearts of cold-blooded animals that the rapidity with which an idioventricular rhythm develops depends in part upon the rate at which the ventricles were beating previously. In studying the behavior of the ventricles when auriculoventricular dissociation was present, Erlanger and Hirschfelder[8] observed that after cessation of ventricular tachycardia produced by electrical stimulation there was a period of slow contraction of the ventricles. The duration of the "stoppage of the ventricles" was found to depend largely upon the duration of the preceding period of artificial stimulation and the rate at which the stimuli were applied, as well as upon a certain "depressed" condition of the heart at the time of stimulation. These observations were subsequently confirmed by Cushny,[9] who stated that, in addition to the rate and duration of stimulation, reduction of oxygen in the perfusing fluid, resulting in asphyxia, and diminution in the amount of the perfusing fluid at such times were probably also factors.

Both Erlanger and Hirschfelder, and Cushny noted that there were two types of ventricular bradycardia following artificial stimulation. In the first type, the first interventricular interval after cessation of

stimulation appeared to be the longest, and in the other type the successive intervals increased in length from beat to beat for several beats before acceleration began.

They further observed that the lengthening of the pauses after cessation of artificial stimulation was generally more marked and more per-

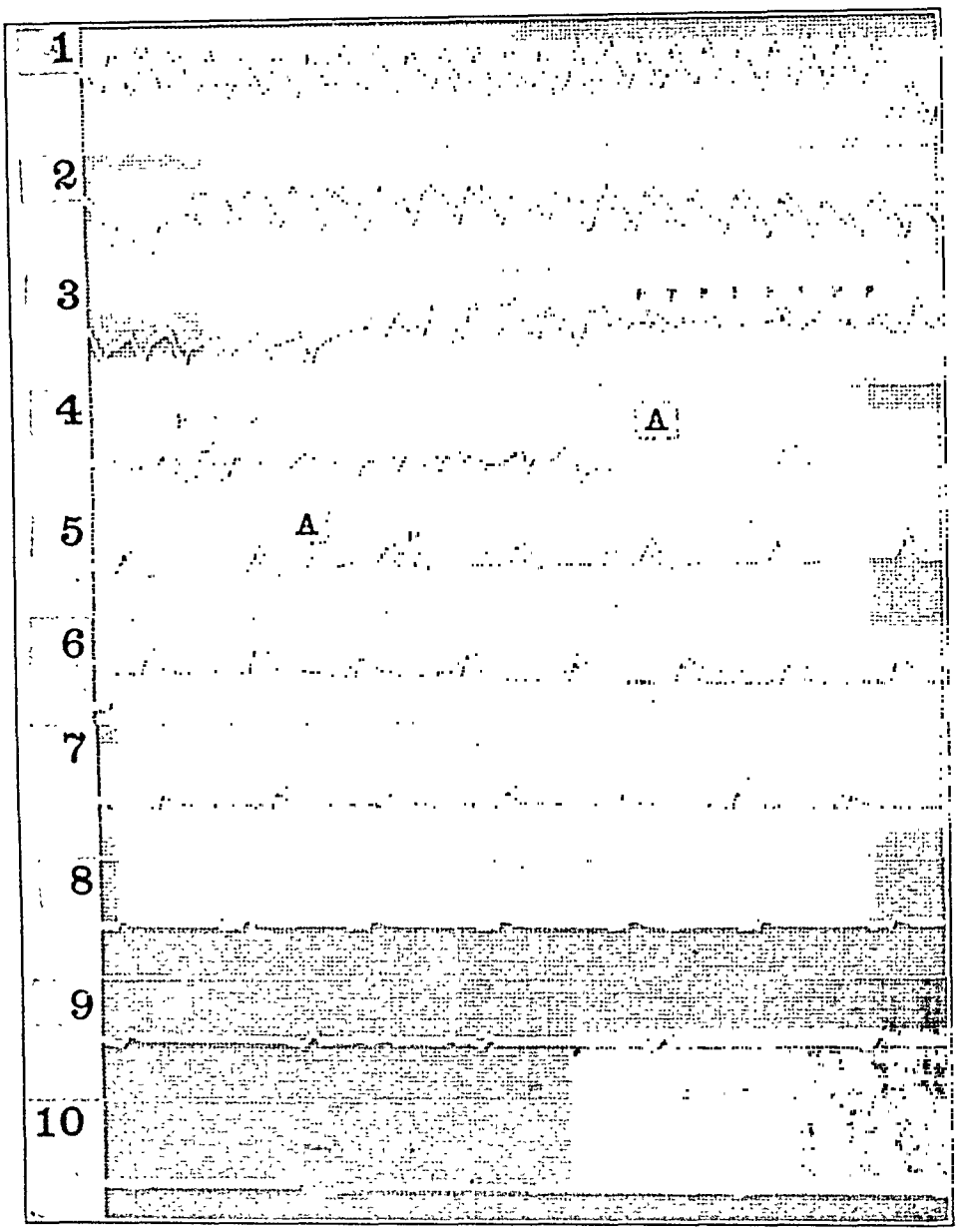

Fig. 1.—Ventricular tachycardia with a ventricular rate of 187 beats per minute.

Fig. 2.—Ventricular tachycardia with a ventricular rate of 150 beats per minute. Auricular activity cannot be made out.

Fig. 3.—Ventricular tachycardia alternating with sinus tachycardia.

Fig. 4.—Slowing of the ventricles and auricles precedes standstill of the heart (*A*).

Fig. 5.—An intermediary idioventricular rhythm with a rate of 41 and only an occasional auricular beat develops shortly after the tachycardia and three minutes after the patient appeared to be dead.

Figs. 6-10.—Variable ventricular rate with regular beating, but with no auricular activity, continues until all electrical activity ceases, twenty-eight minutes after the patient appeared to be dead.

sistent in the latter phases than in the beginning of the experiments. As the "energy" of the heart decreased, the results of the accelerated rate became greater, and a longer interval had to be allowed to obtain the return of the rate prevailing before the interference. Cushny concluded that this slow phase was not inhibitory in origin, since it occurred after, as well as before, full atropinization. He felt that the phenomenon was due to depression of stimulus formation in the ventricular pacemaker, which would be analogous to the fatigue of striated muscle, and that the contractility and excitability of the ventricles were not diminished at such times.

In ventricular tachycardia the auricles beat independently of the ventricles, but at a slower rate. It is conceivable that the rapid beating of the ventricles may progressively augment the fatigue of the ventricular pacemaker and thus lead ultimately to asystole, as in our patient. This would occur more readily if the duration of the tachycardia were such that asphyxia supervened, and in particular if there were heart muscle damage such as our patient exhibited. Theoretically, therefore, the cause of death in patients with ventricular tachycardia should be ventricular asystole, rather than fibrillation.

SUMMARY

In a 52-year-old man with acute coronary thrombosis, and an ectopic ventricular tachycardia which lasted two days, the terminal cardiac mechanism was bradycardia and ventricular standstill. The heart continued to be electrically active for twenty-eight minutes after the patient appeared to be dead. The tachycardia was ended by a long postundulatory pause; thereafter the ventricular rate was variable and auricular contractions were absent until the heart stopped completely. It is very likely that in such patients ventricular standstill is the mechanism of the dying heart as frequently as ventricular fibrillation.

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FUNCTIONAL COR BIATRIATUM TRILOCULARE*

Report of a Case With Malposed Ventricular Septum and Normal Position of the Great Vessels: A Duplicate of the Holmes Heart

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HOLMES,[1] the first Dean of McGill Medical School and one of the earliest leaders in American medicine, described, in 1824, a case of cor biatriatum triloculare with the pulmonary artery and aorta in normal relationship. Neither has Abbott,[2, 3, 4] nor have we, been able to find another reported case that is similar to this heretofore unique heart. We believe that the following case presents a duplicate of the Holmes heart.

CASE REPORT

A white girl, 14 years old, entered the Jewish Hospital Sept. 3, 1937, complaining of headache and stiff neck.

Family History.—The family history was essentially negative.

Past History.—Rapid breathing was noted shortly after birth and this persisted. A thundering precordial murmur was heard by the father, a physician, during the first week of life, and cyanosis was first noted shortly afterward. Clubbing of the fingers and toes became noticeable between the second and third years. The patient was always somewhat undernourished and undersized; otherwise, the developmental history was normal. Her general health had been good, but between the ages of 8 and 10 she had uncomplicated measles and varicella, and there had been occasional upper respiratory tract infections. There was never anything to suggest chorea, rheumatic fever, or endocarditis. Catamenia never occurred. She weighed 82 pounds at the onset of the present illness. The patient was never subjected to electrocardiographic or radiographic study.

Present Illness.—One week prior to admission the patient returned from her vacation, during which she was in good health, although on her trip home it was noted that she was less alert than usual. The following day she had a temperature of 100° F. and complained of a slight headache. Her apathy continued, although when aroused the patient displayed her usual keenness. Three days prior to entry the patient began to vomit and continued to do so several times daily. On the day before admission slight nuchal rigidity, hyperactive tendon reflexes, and poorly sustained right and left ankle clonus were found.

Physical Examination.—Examination revealed a somewhat underdeveloped, but fairly well-nourished, 14-year-old white girl. There was a suffused cyanosis of the entire skin, especially pronounced in the markedly clubbed fingers and toes. The sclerae were injected. The throat was negative except for a cyanotic hue. The heart was considerably enlarged to the left and to the right; a loud blowing systolic murmur was audible over the entire precordium, but was heard best along the left sternal border. The first heart sound was largely replaced by the murmur; the second sound was fairly loud. There was no diastolic murmur or thrill. The

*From the Medical Service and Laboratory of the Jewish Hospital, St. Louis, Mo.
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blood pressure was 108/80. The arteries were readily compressible. The lungs were not demonstrably abnormal. The abdominal examination was negative. There was no edema. Neurological examination revealed that the child was slightly irritable and apprehensive. Examination of the cranial, motor, and sensory nerves revealed no abnormalities. Ophthalmoscopic examination revealed cyanotic discs without papilledema. Nuchal rigidity was present, as were the Brudzinski and Kernig signs. The deep tendon reflexes were equal and active. The right ankle exhibited a transient clonus. There were no abnormal plantar reflexes.

Clinical Diagnoses.—It was thought that the patient had congenital heart disease, probably a defective intraventricular septum, together with meningitis, encephalitis, or even poliomyelitis.

Summary of the Clinical Course.—The temperature ranged between 99° and 104° F., varying about 1° during each day. The respirations, 22 to 40 per minute, were generally regular except for some periods of apnea in the latter days of the illness. The pulse was full, bounding, and not unusually rapid at the onset. Its rate gradually rose during the last two weeks of the illness and then remained between 130 and 140 per minute. Pathologic reflexes were frequently present, but, like the other neurological signs, were evanescent. Nuchal rigidity, an almost constant finding, varied in degree; the patient not infrequently revealed marked opisthotonus. Irritability and occipital headache were fairly constant. Clarity of the sensorium alternated with brief periods of semistupor. During the last few days isolated twitchings of various muscles occurred. A deep mulberry cyanosis, present at all times prior to the illness, varied throughout, being at first aggravated by sulfanilamide therapy and later apparently lessened by secondary anemia. At no time during the course of the illness were any significant changes noted in the heart, and only once, followed the first transfusion, were a few moist râles found at the bases of the lungs. The abdomen remained negative. Brief periods of nausea and vomiting occurred, the vomiting at times being mildly projectile. All therapy was essentially without effect and the patient grew progressively worse. Death occurred early on the twenty-seventh hospital day.

Summary of Laboratory Findings.—The spinal fluid was always cloudy and frequently bloody; the cell count ranged between 1500 and 11,000, with polymorphonuclear cells predominating; the total protein ranged between 78 and 216 mg. per cent and the sugar between 10 and 47 mg. per cent; repeated cultures of the spinal fluid by anaerobic and aerobic methods were negative. The leucocyte count ranged between 12,000 and 22,000. The erythrocyte count fell from 8,890,000 to 4,880,000, and the hemoglobin from 170 to 107 per cent (28.9 to 18.2 gm. per cent). The differential leucocyte count showed a persistent shift to the left with the stab forms ranging from 3 to 10 per cent and the polymorphonuclears from 78 to 90 per cent. The urine occasionally contained acetone and hyaline and granular casts.

Autopsy.—Post-mortem examination led to the following diagnoses: (1) Cor biatriatum triloculare (Holmes type); (2) anomalous insertion of the first, second, and third right intercostal veins into right pulmonary vein; (3) intraventricular (cerebral) abscess with ependymitis of the right lateral ventricle; (4) renal infarction; (5) thromboses of branches of the renal arteries; (6) hyperplasia of the erythroblastic tissue of the bone marrow; (7) multiple capillary thrombi of lungs and kidneys.

The heart lay in a horizontal position. The superior vena cava, which was formed by the jugular, the right azygos, and the subclavian veins, was greatly distended. The largest vein was the left subclavian. The first, second, and third intercostal veins entered the pulmonary vein on the right. These veins lay behind the azygos.

Fig. 1.—Common ventricle from the posterior aspect (four-fifths actual size). Key: *A*, aorta; *B*, aortic valve; *C*, interventricular ostium; *D*, common ventricle; *E*, mitral valve; *F*, papillary muscle between A-V valves; *G*, tricuspid valve.

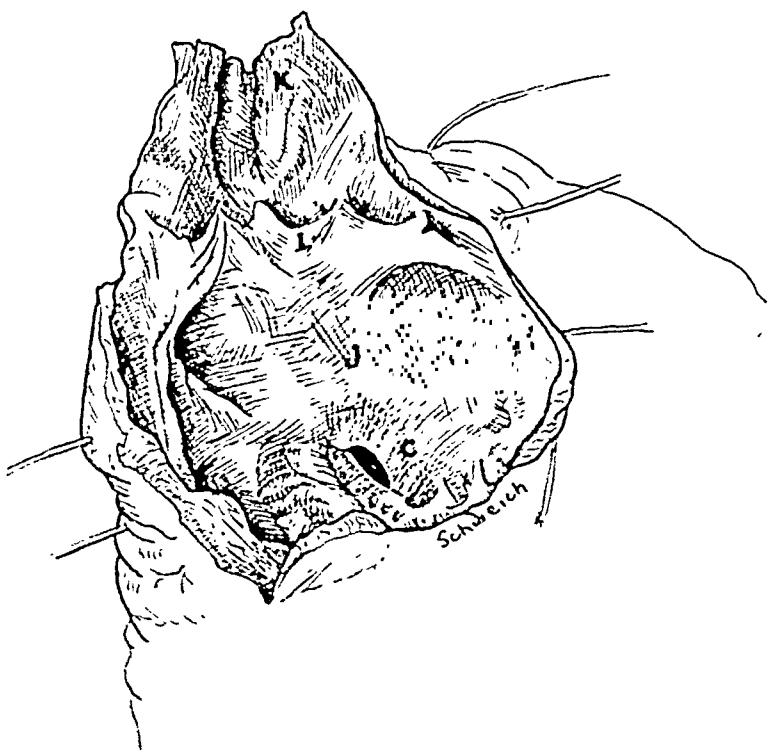

Fig. 2.—Rudimentary cavity (right ventricle) and pulmonary artery from anterior aspect (actual size). Key: *C*, interventricular ostium; *I*, pulmonary valve; *J*, rudimentary cavity (right ventricle); *K*, pulmonary artery.

The heart was broad at the base; it measured 8 cm. from the auriculoventricular groove to the apex. The greatest diameter across the ventricles was 7.5. The apex was blunt and rounded. The surface of the heart presented nothing unusual except for its ovoid shape and a rather marked fullness and tortuosity of the veins of the coronary tree.

The right auricle was moderately dilated and considerably hypertrophied. The venous trunks entered both auricles normally. The interauricular septum was very well developed. The foramen ovale consisted of two dense, broadly overlapping septa of auricular tissue between which a probe could be passed in a posterior

Fig. 3.—Common ventricle from the posterior aspect. Key: *A*, aorta; *B*, aortic valve; *C*, interventricular ostium; *D*, common ventricle; *E*, mitral valve; *F*, papillary muscle between A-V valves; *G*, tricuspid valve.

direction from right to left. The right auricle led into a large, thick-walled ventricle into which the left auricle also emptied. The left auricle presented no abnormality.

The common ventricle had four openings:

1. The tricuspid, communicating with the right auricle.
2. The mitral, communicating with the left auricle.
3. The aortic ostium, which arose posteriorly and approximately in the midline. The caliber of the aorta was definitely reduced, the diameter just above the aortic sinuses being 1.2 cm., and just beyond the left subclavian, 0.9 cm.

4. A small semilunar opening 0.4 cm. below the right semilunar cusp of the aortic valve and 1 cm. below the notch separating the anterior and medial cusps of the tricuspid valve. The entrance to this opening was somewhat funnel-shaped, with an overhanging thickened muscular shelf above it and an oblique concavity sloping into it from below. The opening was approximately 0.5 cm. in length and 0.2 cm. in width.

Directly below the posterior semilunar cusp of the aortic valve was an extremely well-developed muscular cushion which separated the tricuspid from the mitral valve and projected forward at its most developed portion about 0.7 cm.

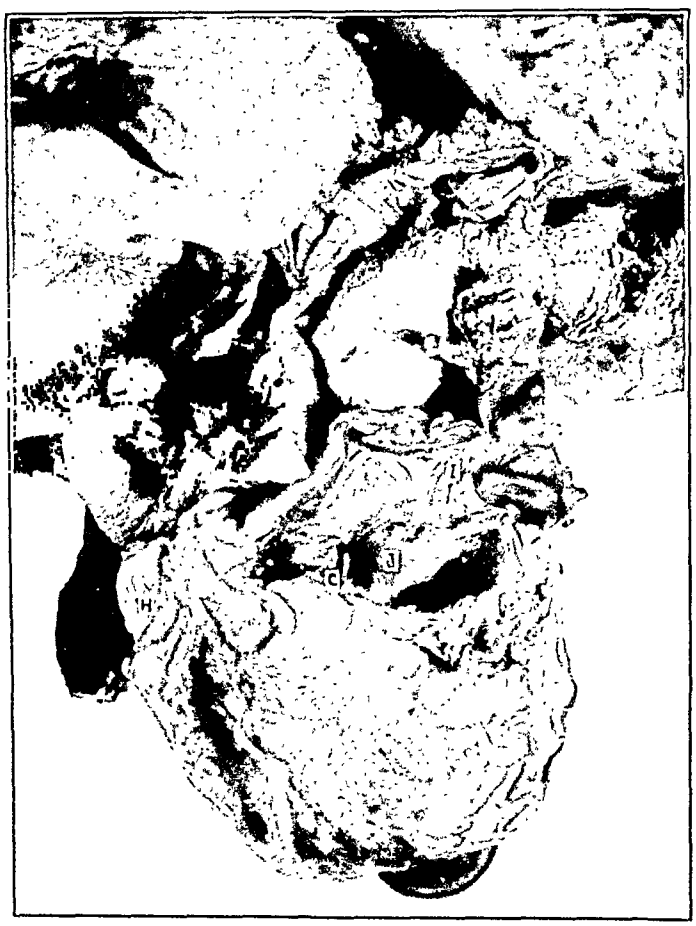

Fig. 4.—Anterior view of heart showing rudimentary cavity (right ventricle) and pulmonary artery in normal relation to the aorta. Key: *C*, interventricular ostium; *H*, right auricle; *I*, pulmonary valve; *J*, rudimentary cavity (right ventricle).

This was the only structure in the common ventricle suggestive of an interventricular septum. The wall of the common ventricle measured 1.5 cm. at its thickest portion. The papillary muscles were well-developed, more so on the left than on the right. The endocardial trabeculation appeared about as it would in the average heart.

The semilunar ostium led anteriorly into a smaller chamber lying at the basal end of the left anterior wall of the common ventricle. The only other opening into this smaller cavity was the ostium of the pulmonary artery. The cavity was roughly globular in shape, with the horizontal diameter a bit longer than the vertical diameter, which measured 1.75 cm.

Beginning between the adjacent edges of the anterior and right cusps of the pulmonary valve was an irregular shelf of thickened endocardium which was ridged and divided in two. The upper part curved superiorly and was soon lost. The lower part coursed downward in a crescentic manner and spread out to form the sides and walls of a shallow pocket at the most lateral part of this cavity.

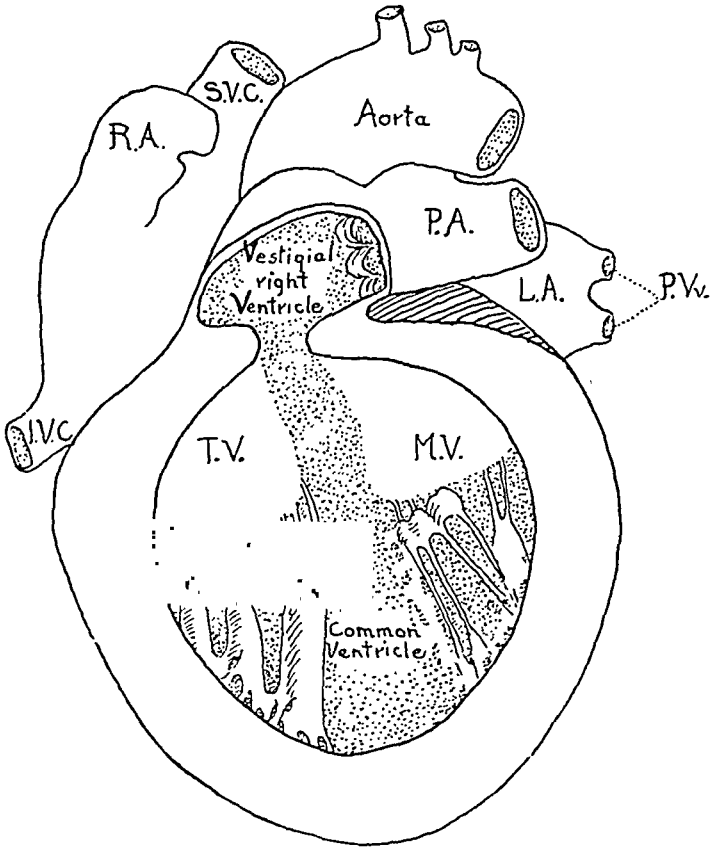

Fig. 5.—Diagrammatic sketch of the heart showing relationships of various component structures.

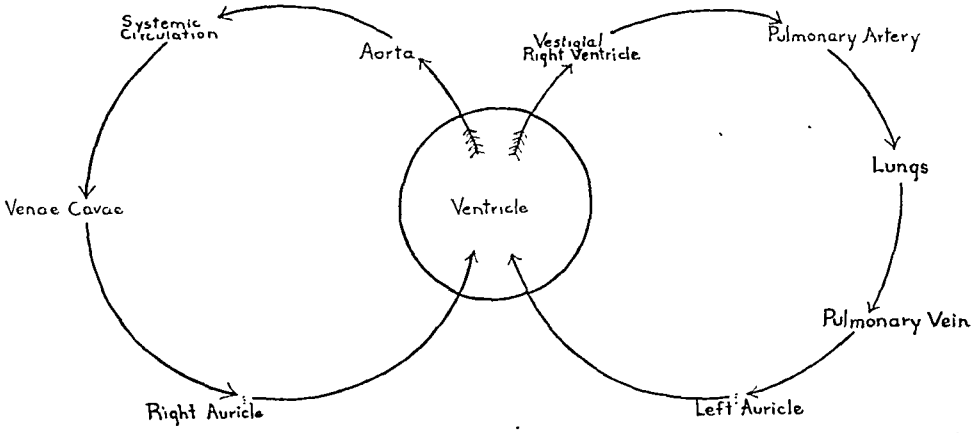

Fig. 6.—Diagram of the circulation in cor biatriatum triloculare (Holmes type).

The cavity was separated from the common ventricle beneath it by the muscular wall, which varied from 0.8 to 1 cm. in thickness. There was nothing unusual about the pulmonary semilunar cusps except that the posterior cusp displayed a hypertrophied nodulus arantii. The pulmonary artery revealed no stenosis or atresia, the diameter just beyond the valve approximating 1.5 cm. There was no communication between the pulmonary artery and the aorta.

DISCUSSION

Cor biatriatum triloculare, according to Abbott's classification,[2, 3, 4] includes all hearts which consist of two auricles and one ventricle, as well as those which have a rudimentary cavity in addition to the ventricle, in which this cavity communicates with the ventricle by means of a septal defect and with either the aorta or pulmonary artery. This latter type of heart belongs in this class functionally, although anatomically it is four-chambered.

Favorite[5] has analyzed the eleven cases which Abbott collected and was unable to find any others in the literature. He sets up the following criteria for classifying hearts as examples of functional cor biatriatum triloculare: (1) A common large ventricle, receiving the auriculoventricular orifices and the orifice of one of the great vessels; (2) defective interventricular septum; and (3) one of the great vessels leading into the rudimentary ventricle. Favorite, adding his own case, found that only seven of the eleven reported cases conformed to his criteria. Since the appearance of Favorite's report we find only one additional case, that of Kornblum,[6] which belongs in this group.

Among these nine cases of functional cor biatriatum triloculare, only one, the Holmes case, presented the untransposed pulmonary artery arising from the rudimentary ventricle. The heart which we have described is the second heart of this type.

Varying interpretations have been given regarding the pathogenesis of the anomalous interventricular septum in the Holmes heart. In Holmes' original report[1] there is apparently no explanation of the anomalous septum and rudimentary cavity. Abbott[7] believes that Holmes must have thought that the septum between these two cavities was the malposed interventricular septum, because he referred to the rudimentary cavity as the right ventricle and to the common ventricle as the left one.

Abbott[7] explains the anomaly by supposing that "at a very early period of fetal life the aortic septum had been continued downwards either to meet the septum inferius, or, that being defective, to meet the opposite ventricular wall, while the septum intermedius failed to close in and complete the division of the cavity. There would have resulted a chamber giving off the aorta and also receiving blood from both the auricles. This latter chamber, which may be considered (in Dr. Holmes' own words) the left ventricle, having thus a great excess of work to do, would have grown much more rapidly than the other. And the wall cutting off the small cavity containing the pulmonary artery would, in the subsequent growth of the heart, have been carried around to the side of the greatly enlarged ventricle and out of all relation to the septum intermedius between the mitral and tricuspid valves. And exactly the appearances seen here would have been reproduced."

Gnai[8] interprets the anomalous septum as being produced by atrophy of the cardiac bulb and hypertrophy of the left ventricle. This opinion is based on his assumption that the bulboventricular sulcus of Davis and the interventricular sulcus are the same.

Abbott's interpretation is criticized by Kornblum,[6] who states that it is difficult to understand "in view of the dynamics of the circulation, how the interventricular septum can be brought across a venous orifice in the development of the heart." Kornblum[6] assumes that the septum develops to the right of the right auriculoventricular orifice. He believes that the posterior border of the septum has grown further to the right than normal and has thus come into relationship with the right bulbar ridge on the right side of the auriculoventricular opening. Then, with further development, the bulbar ridges fusing with one another and with the interventricular septum, the right auriculoventricular ostium would remain in the left ventricle and there would be, on the right, a small chamber without a venous orifice.

SUMMARY

A clinicopathologic report of a case of functional cor biatriatum triloculare duplicating the Holmes type is presented. This is the second case on record.

We wish to thank Miss Sophie Schweich for the drawings and Dr. H. A. McCordock for the photographs.

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Society Transactions

AMERICAN HEART ASSOCIATION, 1938

The fourteenth scientific session of the American Heart Association was held June 10 and 11, 1938, at the Sir Francis Drake Hotel, San Francisco, Calif. Dr. Paul D. White, Boston, Mass., was the chairman of the program committee for the general cardiac session, and Dr. Wallace M. Yater, Washington, D. C., for the Section for the Study of the Peripheral Circulation.

The discussions of the papers presented follow.

General Cardiac Program

Discussion of the paper, "The Reversible Heart," by Dr. Rudolph Matas and Dr. Ben Heninger, New Orleans, La.

Dr. George Herrmann, Galveston, Texas.—The presentation by Dr. Matas and Dr. Heninger on the reversibility of cardiac hypertrophy in arteriovenous aneurysm cases raises several questions. Will pathologic work hypertrophy completely disappear as does the metabolic cardiac change in myxedema or the nutritional myocardial disorder of beriberi? Chemically, work hypertrophy is different from muscle mass increase of metabolic or nutritional origin. How much of the cardiac enlargement in these cases that are completely reversed is due to hypertrophy and how much is due to dilatation? At what stage does the hypertrophy become irreversible? I doubt whether great pathologic cardiac hypertrophy will ever entirely disappear as skeletal muscle atrophies from disuse.

Dr. Idys Mims Gage and I, working under the inspiration of Dr. Rudolph Matas, studied the effects of experimentally produced arteriovenous aneurysm on heart-weight/body-weight ratios. In those animals in which the A-V shunt remained open for only twelve to forty-eight hours there was no hypertrophy. In two animals in which the shunt functioned for six days and fifty-five days and roentgenograms showed cardiac enlargement, there were no increases in heart-weight/body-weight ratios. Other animals with A-V fistulas of 25, 40, 80, and 143 days' duration showed increasing grades of hypertrophy. One which had a shunt for two years and one which had a patent A-V communication for eight years showed tremendous cardiac enlargement.

It will now be necessary to determine how long an arteriovenous aneurysm may be present before it produces irreparable damage. Robbs' new technique for radiologic visualization of the cardiac chambers and for measuring the thickness of the heart walls after the intravenous introduction of diodrast may make it possible to establish and record graphically the essential facts as to the presence and the degree of hypertrophy, as well as dilatation, without sacrificing the animals. The cause of the heart changes may then be removed and the effects recorded at intervals by the same technique.

The indications in the presence of arteriovenous aneurysm, as pointed by Dr. Matas and Dr. Heninger, are for eradication of the fistulous opening or excision of the cirsoid aneurysm as soon as proper preparations can be made. The recurrence of the condition calls for repetition of the surgical treatment, as they have

demonstrated. Their cases show that what appears to be complete reversibility may be accomplished even though symptoms of cardiac failure have been present. There may come a time, however, as noted in their cases, when complete reversibility is no longer possible.

Discussion of the paper, "The *Mechanism Involved in the Production* of Cardiac Hypertrophy: The Effects of Digitalis on Limiting Cardiac Hypertrophy," by Dr. George R. Herrmann and Dr. George Decherd, Galveston, Texas.

Dr. Sprague.—I think this is particularly important in relation to what Dr. Herrmann said originally about the necessary courage for digitalizing patients, that is, slightly poisoning them over a long period of time. Of course, this problem of digitalizing the heart merely because it is enlarged has been quite a moot point in Boston because of Dr. Christian's espousal of that point of view some time ago. It would seem as if the evidence given here were suggestive enough to give us the courage, and the only difficulty may be that our patients will live so long that we shall not be able to study them ourselves if we digitalize them early enough.

Dr. Roy W. Scott, Cleveland, Ohio.—Although this paper presents interesting and suggestive experimental data, it seems to me that one should proceed with caution in using these observations as a basis for digitalizing patients, particularly those with hypertensive heart disease.

Certain it is that digitalis affects neither the renal vascular disease responsible for the hypertension, nor the coronary artery disease present in a high percentage of such cases. Therefore, to keep hypertensive patients without congestive failure mildly intoxicated by digitalis, in the hope of thereby limiting cardiac hypertrophy, does not seem warranted.

Discussion of the paper, "Pharmacological Studies on Cheyne-Stokes Respiration," by M. H. Nathanson, M.D., and J. P. Fitzgibbon, M.D., Los Angeles, Calif.

Dr. Howard B. Sprague, Boston, Mass.—I can confirm the findings in this paper to a certain degree because we have given somewhat over one hundred intravenous injections of this drug in the treatment of Cheyne-Stokes respiration with very satisfactory results. There is one question that I would like to ask, and that is: Have any untoward results been observed in the intravenous administration of this drug, such as transient constriction in the chest, and so forth? I am sure we would all like to hear from others who may have had experience with it.

Dr. Wilhelm Dressler, Vienna, Austria.—I may perhaps say a few words about our experience with aminophyllin, which we have been using in Vienna for more than ten years. We administer aminophyllin either intravenously or by suppositories. The intravenous injection of 7.5 grains is in general well tolerated provided that we inject very slowly and dilute the drug with 10 c.c. of glucose or saline solution.

Aminophyllin, when administered intravenously in cases of Cheyne-Stokes breathing, produces excellent results and relieves dyspnea at once, even when Cheyne-Stokes breathing does not cease entirely. It is important to know that arteriosclerotic patients suffering with Cheyne-Stokes respiration often complain only about insomnia. Frequently in such cases Cheyne-Stokes breathing is not recognized as the cause of the insomnia, since it may be indistinct during the daytime and develops fully only at night. If we are in doubt whether or not Cheyne-Stokes breathing accounts for insomnia in cases with heart conditions and left ventricular failure, it is advisable to give aminophyllin intravenously, or as a suppository at bedtime. A good effect of the drug is sufficient evidence that Cheyne-Stokes breathing was present.

Theophyllin has a similar effect when administered intravenously. We have tried caffeine, too, both orally and intravenously. Its effect on Cheyne-Stokes breathing is satisfactory, but does not last so long as the effect from aminophyllin.

We give 7.5 grains of aminophyllin intravenously once a day, and in severe cases of Cheyne-Stokes breathing even twice a day. The effect lasts for from six to eight hours. Suppositories do not work quite so satisfactorily. Sometimes the injection of aminophyllin is followed by excitement or nausea. Other unfavorable effects we have never seen.

Dr. J. Marion Read, San Francisco, Calif.—We have given aminophyllin intravenously at the San Francisco Hospital, and I can confirm what has been said about the almost immediate cessation of the cyclic breathing. There were no ill effects; but in our estimation its effect was rather short-lived. If it lasted fifteen minutes to a half hour, we considered that we were getting a fair result; that was the longest it lasted in any of the instances. We gave it, hoping we could stop this nocturnal cyclic breathing which is so disturbing; but we discontinued it because we found the effect was not sufficiently long-lived to warrant its continuance.

Dr. Nathanson (closing).—We did see a few reactions, but none were serious. In several instances, the injection was followed quite promptly by flushing of the face, sweating, nausea, and increase in heart rate. I did not cover in our report some observations on therapy directed at the prevention of nocturnal dyspnea and restlessness, such as were mentioned by Dr. Dressler. A typical case that I have in mind is that of a patient with hypertension who is comfortable during the day, shows no evidence of pulmonary congestion, and has a vital capacity of 4000 c.c., which is practically normal for this patient. Yet periodically this patient is disturbed at night by marked restlessness with respiratory distress. In this case and in several of a similar type, theophyllin in special enteric tablets was administered late in the day in large doses. The amount used was usually 0.6 gm. to 0.8 gm. in divided doses. The results obtained indicate that there is a place for the oral use of theophyllin compounds in the prevention of nocturnal restlessness and respiratory distress.

Discussion of the paper, "Hypertensive Heart Disease: A Clinical and Pathological Study of 369 Fatal Cases," by Dr. Francis D. Murphy, Milwaukee, Wis.

Dr. D. J. Glomset, Des Moines, Iowa.—I have been very much interested in the paper just presented by Dr. Murphy because recently I have examined rather minutely the coronary arteries of about one hundred hearts for the purpose of determining the degree of arteriosclerosis present. There were over thirty hearts from patients with hypertension in this series. Approximately one-half of them showed only slight arteriosclerosis. The arteries of all were very large. Hence it is logical that the capillaries should also be large. A search for arteriolosclerosis was also made, but none was found.

Discussion of the paper, "The Application of Tomography in the Demonstration of the Pulmonary Anatomy," by Dr. Alexander Petrilli, San Francisco, Calif.

Dr. William J. Kerr, San Francisco, Calif.—Dr. Petrilli's contribution is a very important one. I can see great possibilities in anatomic study by comparing his films with frontal sections made after death, along the lines followed a good many years ago by Norris and Landis, of Philadelphia. Certainly we shall be able to clarify a good many of the pulmonary findings in patients with enlarged auricles compressing the arterial branches; details of the vessels would be more readily seen; and we should be helped in other conditions, such as aneurysms of the pulmonary artery, obstructions of arteries by tumors, and a great many other conditions.

I think it is a very interesting approach to this study.

Dr. Petrilli (closing).—There are different ways of obtaining these sections, as you probably all know; this is the method known as tomography, in which the tube moves in one direction only; there are other variations of this apparatus which give essentially the same results. There will undoubtedly be a long period of discussion lasting over many years as to which method is the best, but eventually we shall use the one that we like.

Discussion of the paper, "Calcareous Disease of the Aortic Valve," by Dr. Frederick Willius and Dr. Thomas J. Dry, Rochester, Minn.

Dr. William Stroud, Philadelphia, Pa.—In the cases of this disease that we have had in Philadelphia, we have been very much impressed with the excellent prognosis. I am sure, as Dr. Willius has said, that we are going to be more and more surprised as we look for these calcareous changes in the roentgenograms.

Dr. Louis Faugeres Bishop, Jr., New York, N. Y.—In studying the bicuspid aortic valve, following the method described by Lewis and Grant, we found it possible to differentiate a congenital raphe or a fused commissure ridge in aortic valves which were the seat of advanced calcification and stenosis.

I wanted to ask Dr. Willius whether he has encountered congenitally bicuspid aortic valves in any of his examples of calcareous disease.

Dr. Willius (closing).—We did not encounter any case of bicuspid aortic valve in this series. There was one very interesting case, however, which I would like to mention. Complete fusion and calcification of the three cusps had occurred, resulting in complete obstruction of the orifice, and through a fortuitous circumstance a small fenestration in one cusp occurred, which was the only communication between the left ventricle and the aorta.

Discussion of the paper, "Dehydration Through Glycosuria: Experiments With Phlorhizin as a Diuretic," by Dr. Wilhelm Dressler, Vienna, Austria.

Dr. Charles N. Hensel, St. Paul, Minn.—I have been much interested in listening to Dr. Dressler's report on the use of phlorhizin as a diuretic because I have at the present time a patient with an intractable edema who might benefit from the use of this remedy. She is an elderly diabetic who came in with acute congestive heart failure and hydrothorax requiring thoracenteses. She was placed on a regular diet and insulin but continued to be troubled by dropsical accumulation. For a long time salyrgan was successful in bringing about diuresis. When the veins became sclerosed, mercupurin was substituted. Within the past few months albumin and casts are appearing in the urine in increasing amounts, evidently due to the mercury radical in the mercupurin.

It seems to me that phlorhizin might be distinctly beneficial in this particular patient, provided it does not produce liver damage. As I recall, Dr. Dressler stated that the diuretic action of phlorhizin arose through preventing the resorption of sugar in the urinary tubules. If this is so, may we not have to watch the level of blood sugar, which may be reduced to a point of hypoglycemia as a result of the action of phlorhizin?

Dr. Wilhelm Dressler (closing).—As to diabetes, it has been advised to give phlorhizin in order to lower the blood sugar level. I have used phlorhizin as a diuretic in one diabetic case, and it produced an excellent diuresis.

German and American authors have repeatedly emphasized that phlorhizin is harmless in the doses ordinarily used. Nevertheless, we ought to be very careful until we have gained more complete experience, both from animal experiments and from treatment of patients, to be sure to avoid any injury to the patients.

In the case of ascites mentioned above, I would try to administer mercupurin intraperitoneally; this therapy sometimes gives excellent diuretic results.

Discussion of the paper, "Incidence of Coronary Disease in Cases Autopsied at the Massachusetts General Hospital," by Dr. W. H. Gordon, Dr. Edward F. Bland and Dr. Paul D. White, Boston, Mass.

Dr. Howard B. Sprague, Boston, Mass.—This paper can be considered an early step in the attempt to determine some of the factors which are responsible for arterial change from a point of view of economics and of some of the wider aspects of the problem.

I just want to mention that if any of you in your travels throughout the world have any opportunity to study social conditions in which a people is set up definitely into layers, it may contribute considerably to progress in this analysis. I mention this particularly in relation to an observation that Dr. White made on his recent trip to Mexico, where he felt that the people were divided very clearly into two completely separated economic and social groups with respect to the manner of living and nutrition, so that there are opportunities to study this subject in man under conditions which rather closely approximate animal experiments.

Discussion of the paper, "The Prognosis of Bundle Branch Block," by Dr. Louis Faugeres Bishop, Jr., New York.

Dr. William J. Kerr, San Francisco, Calif.—It probably would be of interest if Dr. Bishop would say something about the life expectancy in this group of patients who survived.

Also I would like to ask him a question, that is, whether syphilis played a very considerable role as the cause of death in the younger age group of those who suffered from this condition.

Dr. John J. Sampson, San Francisco, Calif.—The prognosis for patients with bundle branch block that Dr. Bishop gives confirms the opinion which was given by Miss Nagel and myself, based on three hundred cases that were studied at the University of California Hospital about three years ago. The fact which he demonstrates, in agreement with our data, is that the individuals destined to die do so fairly soon after the discovery of the lesion; such seriously ill patients increase the fatality rate of the entire series.

In our particular series the number of patients who died rose very rapidly within the period of the first year. Between the first and third years, the curve of mortality was definitely less steep, and after the fifth year the curve flattened out very much as Dr. Bishop's curve did.

We likewise reported one case of seventeen years' duration. There were a few other interesting observations in our series which were not noted by Dr. Bishop, namely, that it is extremely rare to find bundle branch block in cases of congenital heart disease and that the commonest occurrence of bundle branch block was in coronary arteriosclerosis.

I would like to hear Dr. Bishop's statement as to his estimate of possible life expectancy in patients with this lesion. We determined our life expectancy in our series of cases and found that if these individuals lived over one year after the discovery of the bundle branch block their chances of a normal life expectancy increased approximately 50 per cent, and again increased approximately 25 per cent within the next two years. If a patient had survived approximately five years after the time of the discovery of his bundle branch lesion, we found that the bundle branch block alone would have practically no influence on his life expectancy.

Dr. Oscar F. Johnson, Sacramento, Calif.—In the first place I want to compliment Dr. Bishop on his excellent paper. We ordinarily think of bundle branch lesion as due to arteriosclerosis or syphilis. At this time I should like to state that I have a 43-year-old patient under observation who has a bundle branch lesion. When

I first saw him, he was referred to me because of tingling and numbness in his fingers. He often awakened at night with a choking sensation. He was examined very carefully, but there was no demonstrable cause for his bundle branch lesion. He stated that about eleven or twelve years ago he was in an automobile accident. He sustained a terrific steering-wheel blow across his chest. He was unconscious for a few hours. Recovery was uneventful. I mention this case because I think the cause of the bundle branch lesion was trauma. During the past year the patient has enjoyed excellent health except for moderate shortness of breath.

Dr. Howard B. Sprague, Boston, Mass.—I think I will have to say something in an attempt to explain some of the rather crude figures of an earlier day.

Dr. Bishop reported cases, about nine hundred in number, and a third of those are the ones reported by Graybiel and myself some years ago with a mortality much higher than he reports.

It seems perfectly clear, I think, and we would all agree with his conclusions, that it is the underlying degree of cardiac disease which is the important factor in the prognosis. We have come to believe that bundle branch block, when it is merely a part of the whole coronary involvement, does not really add so much to the gravity of the prognosis.

But there are constantly appearing instances in which bundle branch block apparently is the result of a very localized coronary occlusion of smaller vessels which supply the conduction system alone, and therefore does not indicate such a poor prognosis. After all, is not this another example of what happens when one takes electrocardiograms on a lot of people suspected of cardiac disease, instead of a lot of people who have obvious cardiac disease, as was done in earlier series?

Undoubtedly, we shall find many patients with bundle branch block who will live for a long time. It is very much like coronary thrombosis in general.

Not so many years ago, we had the idea that everybody who had coronary occlusion died. Now, by taking electrocardiograms on everybody who has a pain in his stomach, we find "coronary" T-wave changes, and we know a great many people recover and live for years.

Bundle branch block is not a pleasant thing to find in anyone, just the same; 58 per cent of Dr. Bishop's patients are dead, and I would not advise the insurance companies even now to consider this a very good risk group.

Dr. Bishop, Jr. (closing).—I want to thank the discussants for their very interesting discussion.

First, I want to apologize to Dr. Sampson for not including his cases. He has arrived at the same conclusion, that, if these patients survive a few years with bundle branch block, their chances seem to be greatly increased.

With regard to the question of syphilis, only two patients in our series had syphilis. These were observations from private practice where cardiovascular syphilis is relatively rare.

I can only agree with Dr. Sprague entirely in what he says that as the result of the development of cardiology we are now taking a great many more electrocardiograms, and our viewpoint is changing about prognosis in general. I believe that the underlying heart disease is the important point.

Discussion of the paper, "The Relationship of the Early Treatment of Syphilis to the Later Development of Evidence of Cardiovascular Syphilis," by Dr. W. P. Thompson, Los Angeles; Dr. W. J. Comeau and Dr. Paul D. White, Boston, with the assistance of Dr. J. McMillan, Dr. B. Wise, Dr. W. C. Reed and Dr. W. H. Gordon.

Dr. J. C. Carr, Chicago, Ill.—I am particularly interested in this paper because the authors have discussed a subject to which we gave much attention several years ago at the Cook County Hospital.

We studied the autopsy reports for two years with the cooperation of Dr. Jaffe and found that in this period syphilitic aortitis was noted 229 times. Aortic regurgitation was responsible for the death of about 13.5 per cent of this group, and autopsy revealed the presence of well-developed aortic regurgitation in 16 other cases, a total of 49, or 21.6 per cent. In 53 instances, or 23.2 per cent, aortic regurgitation or aneurysm was responsible for death.

Now, the interesting thing to us was this: In this large group, no single patient had reported adequate treatment. One patient, a woman with syphilis of the nervous system, reported that she had had twenty-eight "shots." This woman and another woman with neurosyphilis had some treatment for late disease, but no early treatment whatever. My recollection is that there were only nine patients in this entire group who reported that they had ever had treatment.

To us it appeared that the result of this study warranted one statement, viz., that the late results of syphilitic aortitis, the types of cardiovascular disease which are responsible for the death or for the incapacitation of these patients over some years, are wholly preventable. That is the reason I want to emphasize what the authors concluded from a different approach.

Our statistics were based upon the records of the Cook County Hospital. So far as private practice is concerned, we see cardiovascular syphilis only occasionally. It seems to me that the one important lesson we need to bear in mind wherever we are working is that patients with neglected syphilis stand a very good chance of dying, within some twenty years after the initial infection, of some form of cardiovascular syphilis.

So far as these statistics were concerned, 26 per cent did die of syphilitic aortitis and its complications on an average of 22 or 23 years after the initial infection, and in another 14 per cent anatomic evidence of well-developed complications of syphilitic aortitis was discovered at autopsy.

Section for the Study of the Peripheral Circulation

Discussion of paper, "Tissue Pressure: An Objective Method of Following Skin Changes in Scleroderma," by Dr. William A. Sodeman and Dr. George E. Burch, New Orleans, La.

Dr. Winchell McK. Craig, Rochester, Minn.—One of the great difficulties in attempting any therapeutic measure for chronic conditions such as this is the evaluation of results. And I think one of our great difficulties in attempting to treat scleroderma has been the fact that we had no method, or measuring stick, by which to judge our results.

This ingenious method certainly opens up possibilities and allows us to evaluate the results following operation in a quantitative way and, as has been depicted on the screen, we do not have to wait to evaluate it by observation.

I am tremendously interested in this and think it has a very important place in the treatment of scleroderma.

Dr. A. W. Duryee, New York, N. Y.—A year ago before this Section we reported from the Post Graduate Hospital thirty-four cases of scleroderma, in twenty-seven of which the patients had been treated by mecholyl, and at that time the only means of demonstrating improvement was increased motion and flexibility of the skin.

Following some suggestions at that meeting, we have attempted during the past year to measure tissue pressures and skin conductivity. At this time we are not prepared to give a final report, but the thing that strikes me in all of the work we have done so far is that with improvement in certain areas sclerodermous patches develop in other areas, so that in order to check up carefully on any individual many

readings must be made over the various parts of the body, and although you may record a drop in tissue pressure in any one place, it may mean a marked increase in another location.

I think we have from this paper some very interesting data that we can use in further checking results.

Dr. Sodeman.—This method and the determination of tissue pressure throw light as well upon the mechanism of the vascular changes in scleroderma. The changes are supposedly of two types: one, a primary change, with secondary scleroderma, and the other, a secondary vascular change.

You can see from the figures thrown on the screen that some of these values are higher than the normal capillary pressure. Thus in order for the circulation to be adequate, pressure would have to build up from the arterial side and increase the capillary pressure and the venous pressure in order to complete the circulation through that part. Apparently, therefore, the elevations in tissue pressure are important in the vascular changes which occur secondary to the sclerodermous process. It is difficult to insert needles into veins in the dorsum of the hand in a patient with a thick skin. We have accidentally punctured veins in sclerodermous areas and made determinations of venous pressure upon those individuals, for this apparatus can determine venous pressure as well. We found that the venous pressure was elevated in those areas in which the tissue pressure was markedly elevated, whereas a determination of the venous pressure closer to the heart showed that the venous pressure was in the normal range in areas in which the scleroderma did not occur.

Dr. I. H. Page, Indianapolis, Ind.—I would like to ask Dr. Burch how constant these readings are, that is, over a period of time, in the same place. Are the figures in the first column the average of all the results of one reading? If so, how constant are those readings from day to day?

Dr. Burch (closing).—In all our determinations we make three readings. These readings have always agreed within ±1 mm. of water. In normal individuals we have made determinations from day to day in the same area and found variations no greater than 4 mm. of water.

In making repeated determinations we should be careful to use exactly the same area. As has been mentioned, there are variations from area to area, and, since scleroderma is a rather patchy disease, if we do not use the same area we are likely to obtain results which will not agree. And, of course, the more determinations we make in different areas the more valuable the information.

Discussion of the paper, "Bilateral Carotid Sinus Denervation in a Patient Having Syncopal Attacks and Congenital Vascular Anomaly," by Dr. Albert H. Elliot, Dr. Neville T. Ussher, and Dr. Caleb S. Stone, Santa Barbara, Calif.

Dr. Morris H. Nathanson, Los Angeles, Calif.—The report presented by Dr. Elliot and his associates describes a rather unusual type of syncope associated with a sensitive carotid sinus.

There is no question that a sensitive carotid sinus may be the basis for attacks of syncope. In an individual suffering from dizziness or syncope in whom the characteristic symptoms may be reproduced by carotid pressure, there is little doubt that the diagnosis is carotid sinus syncope. However, there are many individuals, especially elderly men, in whom carotid sinus pressure produces prolonged cardiac standstill and syncope, who never develop spontaneous attacks due to cerebral ischemia. In fact, in a routine study of the carotid sinus reaction, I found about 60 instances of extremely sensitive carotid sinus reactions on repeated testing. On

questioning these individuals, it was found that dizziness or syncope occurred in less than 10 per cent. It is, therefore, possible that syncopal attacks and a sensitive carotid sinus may be present in an individual with no etiologic relationship between the two.

I have studied for the past four years the action of drugs on the cardiac standstill which can be induced in many individuals by pressure on the carotid sinus. The only substances which are effective are adrenalin and chemically related compounds, the sympathomimetic amines. Recently, I have studied a new compound of this group, paredrine (parahydroxyphenylisopropylamine); this compound is stable, effective on oral administration, and about two to three times as active as ephedrine. Paredrine also has an advantage in that it does not produce the unpleasant side effects of ephedrine. I have treated several patients suffering from syncopal attacks associated with a sensitive carotid sinus with this drug and have had favorable results.

I have, up to recently, not observed any harmful effects from the testing for the response to carotid sinus pressure and have carried out this test on several hundred individuals. Recently, however, a patient entered the hospital with a history of syncopal attacks. The resident, suspecting a sensitive carotid sinus, very properly tested the patient by pressure over the carotid sinus. A cardiac standstill of several seconds followed, associated with jerky movements of the right arm and leg with the development of a right hemiplegia.

Discussion of the paper, "Factors Influencing Blood Pressure Determinations: Accommodation to Postural Change and Transient Differences in the Two Arms," by Dr. Eric Ogden and Dr. Nathan W. Shock, Berkeley, Calif.

Dr. W. D. Stroud, Philadelphia, Pa.—For the past eight years, I have been taking the blood pressure in both arms of all patients that have come to me, and I can confirm the impression that has been given by this last paper, namely, that there is quite a marked difference in the blood pressure in the two arms in a vast majority of cases.

Of course in an office examination one cannot control all the factors involved as well as they have been controlled in this presentation.

The main reason I have taken the blood pressure in both arms is that eight years ago, before the insurance companies had stopped granting total disability insurance, one of Walter Camp's "all-American" football players took out life insurance containing a total disability clause. His blood pressure was taken by the insurance doctors in the left arm only. His was a $250,000 policy taken up by three or four companies. This individual had a blood pressure of 120/80 in the left arm. Three weeks after he took out this policy, a cardiac infarct developed while he was playing golf. I saw him six weeks after this infarct occurred, and at that time he had a blood pressure of 120/80 in the left arm, but a pressure of 200/110 in the right arm. Presumably then, if these companies had taken the blood pressure in both arms, this gentleman would not have been living in Santa Barbara for the last eight years on his income from this total disability insurance!

Also, I think it is a very good procedure since nowadays all the general practitioners have electrocardiographs and know as much about cardiovascular disease as we do, and yet few of them take the blood pressures in both arms. If we, as cardiologists, when seeing patients in consultation, take the blood pressure in both arms, then, at least, we have done *one* thing the average general practitioner does not do!

Discussion of the paper, "The Precision of Individual Blood Pressure Measurements," by Nathan W. Shock, Ph.D., and Dr. Eric Ogden, San Francisco, Calif.

Dr. Ogden.—I do not think there is much to be added to this, except to repeat the warning that Dr. Shock gave. We have been making studies in which we hope to use pulse pressure measurements for computation of metabolic rates, according to Dr. Read's formula, and for other purposes, and therefore it was important to see how precisely they could be made.

This indicates the best that we can do. It is not an indication of precision which any of those three observers can expect to get in a casual, clinical measurement. It represents the best that they can do, and I certainly hope there will be no misinterpretation of that. None of us feels that there is a possibility that in the ordinary way our systolic pressure measurements are good to 1.5 mm. of mercury, because they certainly are not.

Another thing is this: the last curve that Dr. Shock displayed shows very effectively the necessity of making three or four readings and the comparative increase in worth of making ten or a dozen readings to assess a particular blood pressure.

Everybody in this group has found by experience, doubtless, that a single reading is useless and that three or four readings are valuable. One value of determining this quantitatively is, I think a matter of teaching, inasmuch as the young man who is just learning to take blood pressures is inclined to be less skeptical of proof like this than of a statement of clinical experience. If somebody says, "I find that it is necessary to take three or four readings," he is likely to doubt it and to want to learn it himself. If you can show him by a statistical presentation why it was necessary to take three or four readings, he is going to save quite a good deal of time which he would spend in learning over for himself the things which have already been learned by other people.

Discussion of the paper, "Factors of Error in Blood Pressure Readings," by Dr. Irving S. Wright, Dr. Ralph F. Schneider, and Dr. Harry E. Ungerleider, New York, N. Y.

Dr. Eugene S. Kilgore, San Francisco, Calif.—I am so amazed by this paper that I hardly know where to begin the discussion. To explain, it will be necessary to go back a number of years and describe certain personal experiences. I had undertaken a research among college students which required many blood pressure measurements under varying conditions. Desiring an impeccable technique, I consulted the physiologic and the clinical books and found them united in regarding the Erlanger instrument as the most accurate. It furnishes graphic oscillatory indices for systolic and diastolic points, and the readings are made from a mercury column at the moment when these oscillatory phenomena appear on the smoked drum. In my work this necessity for hasty judgment was eliminated by including on the graphic record a curve showing the changing mercury manometer level simultaneously with the pressure oscillations. Since I fancied the personal factor of error was thus entirely eliminated, I was later much annoyed to find that I could not honestly decide just where the systolic and diastolic criteria appeared on most of the oscillation graphs. Study only increased the confusion; but at length, overcoming my feeling of inferiority, I changed the direction of the research, making it a study of the personal factor of error in the oscillatory blood pressure method—not among novices but among well-known professors of medicine and of physiology. A half dozen of them, including Professor Erlanger himself, served as subjects of the experiment. Each received a photographic copy of the same one hundred oscillation graphs selected at random, and returned the copy after

marking systolic and diastolic reading points. These individual reading points were then assembled on a fresh copy and were expressed in millimeters of mercury. There were discrepancies aplenty. In fact the reading points of different observers were scattered all over the graphs, and in some cases the diastolic reading of one man was actually higher than the systolic reading of another. In continuing the experiments it was shown that one individual (a chief exponent of the oscillatory method) could not mark a second copy of the same one hundred graphs without considerable deviation from his first marks. And the conclusion was inescapable that the oscillatory method was enjoying a most unmerited reputation for reliability.

With several associates I then studied the personal factor of error in the use of the palpatory and the auscultatory criteria. It was found to be comparatively small in both of these methods. And, contrary to another general assumption, it was found that for systolic readings the personal error factor was substantially the same for the auscultatory method as for the original and simple palpatory method. To be sure, the auscultatory readings average a little higher than the palpatory, but that is of no practical consequence. Consistency is all-important; and it was apparent that the net result of a great deal of work and writing had been to introduce and popularize techniques which did not improve consistency of readings, but in some cases had a very contrary effect.

Well, all this was sent on and published in the *Archives of Internal Medicine* in 1915. Just the facts. It seemed superfluous to state the obvious inferences: that the oscillatory method should be given up altogether and that for systolic readings the simple, convenient and nearly fool-proof palpatory method should be readopted as standard for ordinary clinical use and for insurance examinations. For it had already been pointed out that the arterial sounds are not infrequently deficient or absent in the vicinity of systolic pressure—the so-called "auscultatory gap." And the fact is that gross errors in reading systolic pressure by the auscultatory technique are not uncommon.

Our findings have never been controverted. But were these inferences reflected in general practice? Not at all. On the contrary a new graphic oscillatory machine appeared on the market, without pretending to obviate the errors we had found so great in the oscillatory technique; and, favored with an efficient sales force and the always potent appeal of a very high price, it enjoyed wide acceptance. And those who cannot afford or cannot conveniently carry about the oscillatory machine almost invariably continue to rely on the arterial sounds for systolic readings. Some maintain that auscultatory systolic readings should be "controlled" by the finger on the radial artery, but in practice this is rarely done.

These authors have performed the very important service of focusing attention upon an important and much neglected topic. The data assembled show shocking lack of agreement on blood pressure technique among teachers of medicine. But to me the amazing fact is the continued neglect of the palpatory method for systolic readings. The authors of this paper have repeated experiments similar to mine for the auscultatory method and have found the personal error factor about what I found it—an appreciable but clinically not very important error in the general run of cases. But they have not reckoned with the occasional very large error of the auscultatory method for systolic readings, and they have not even considered the use of the palpatory method in which the personal error factor compares favorably with that of the auscultatory method and in which the occasional very large error does not occur. And finally, the most amazing of all is the neglect of insurance companies to insist on the palpatory method for systolic readings, for this is a neglect which costs them money.

Dr. Carl J. Wiggers, Cleveland, Ohio.—There are several compelling reasons why I ought to make a few comments:

1. I am responsible for initiating the instruction in methods for determining human blood pressure at Western Reserve University Medical School. This is a function of a physiology department. No student is promoted to clinical years without a practical test as to his ability to measure blood pressure in accordance with several criteria. In addition, they profit from experience in clinical years, so that instruction is not at fault.

2. I also have had various experiences that can be added to those enumerated today which indicate confusion as to methods for determining blood pressure. In examining National Board candidates, I am usually surprised to find how my blood pressure fluctuates. Again, in three successive examinations for life insurance my systolic pressure was read as 120, 140 and 180 mm. Hg by three examiners for different companies. The last reading was obviously a technical error, and I could not resist the suggestion that if the cuff were applied on the inside of the arm rather than the outside, it would be easier to compress the artery against the bone than to bend the bone toward the artery. This illustrates that careless technique rather than the criteria may be at fault.

3. Few physicians (or investigators) keep in mind the limitations set by the criteria utilized to estimate systolic and diastolic pressures. As tested by hypodermic and optical manometers, systolic and diastolic pressures in the large arteries vary from beat to beat. With normal respiration and rhythmic heart action the variations easily reach 10 mm., while during dyspnea and marked cardiac irregularity the differences are so extreme that no single figure has any significance. Since even normal blood pressure varies in this way, refinements of technique or statistical analyses which claim to measure pressures with an accuracy greater than 5 (or 10?) mm. Hg merely result in delusions of a degree of accuracy which does not exist. However, clinical measurements are still useful even if errors of 10 mm. are incurred.

4. I have checked, over a period of years, a large number of different criteria and also various instruments purporting to make readings more exact. I still feel that the auscultatory method is *generally* the best. We teach that the first sound heard on decompression signals the *highest* systolic, and the appearance of all sounds, the *lowest* systolic pressure during respiration or arrhythmic cycle. However, as Dr. Kilgore suggests, these should always be checked by the palpatory method, for instances occur clinically in which the readings by the latter method may be higher. The auscultatory method is not applicable under certain conditions. Similarly, determinations of diastolic pressure by use of the 4th phase of "decompression sounds" should always be checked by complete disappearance of sounds, and if these do not agree within 5 or 10 mm. the diastolic pressure reading is doubtless faulty. For example, notations of diastolic pressure readings of 15 or 0 mm. in aortic insufficiency are absurd; they are dynamically impossible.

5. Finally, I question whether improvement in the utilization of criteria and employment of apparatus is likely to be achieved through rules promulgated by committees or assemblies. Different criteria must continue to be used under different conditions. We ought rather to seek means for awakening the conscience of physicians to the need of exercising every care. State legislatures or Congress might even pass laws defining the procedures that physicians must follow; but such laws would not make our pressure readings any more exact. Physicians will always insist on freedom to use methods which they individually believe to be the best.

Dr. W. J. Kerr.—I do not know how much Dr. Wiggers' conscience is bothering him this morning, but if it is not troubling him, it probably will be. If the American Heart Association appoints a committee to study the standards for making blood pressure estimations, we certainly hope that men like Dr. Wiggers, Dr. Erlanger, and Dr. Kilgore, who may be protagonists on certain points of view, would be on that committee.

I am certain we do not want to bend any bones in order to get the readings of blood pressure, but we hope to have a committee who will study this and, if necessary, set up some standards that we may be able to follow.

I am sure if Dr. Wiggers' students are like ours, when they get out they have about as many different methods as there are students.

Dr. Ungerleider (closing).—I want to thank the various discussers, and especially Dr. Kerr for coming to my rescue.

If I did not mention anything about the palpatory method as far as the medical schools are concerned, it is because the medical schools themselves did not mention it in their questionnaires. The three replies which did mention the palpatory method of taking blood pressure were those from three insurance companies.

Further, our paper was simply an exposition of the methods taught and used. We did not start out to say which method was the best to use. Being a life insurance medical director, I am at a disadvantage here, of course, but nevertheless, I do feel that we ought to have some standard method of measuring blood pressure.

We do find that mortalities vary with various small increases in blood pressure. Life insurance companies have just concluded a mortality study of over 900,000 people, and it is a rather interesting fact that with every 5 mm. of increase over the average blood pressure the mortality has increased, so much so that, when you leave the accepted clinical limit (I am saying that with a question mark) of about 145 millimeters of mercury, mortality increases by large amounts.

We in life insurance feel that there should be some method by means of which all concerned will talk the same language, that if a reading is designated a systolic reading, we have some idea of where it was read, and if it is diastolic, where that was read.

I feel that Dr. Wiggers is probably correct when he said that we should not be regimented by any committee, but I do, nevertheless, believe that some start should be made.

Discussion of the paper, "The Sulphocyanates in Hypertension," by Dr. M. Herbert Barker, Chicago, Ill.

Dr. Winchell McK. Craig, Rochester, Minn.—I should like to ask Dr. Barker about his experience with the administration of sulphocyanates after splanchnic resection in order to round out his very interesting observations. These post-operative studies are important as they may play a part in the ultimate treatment of hypertension.

Dr. Louis Faugeres Bishop, Jr., New York, N. Y.—I should like to ask if there have been any electrocardiographic observations during the course of this study which would lead us to believe that the cyanate therapy has a direct effect on the myocardium.

Discussion of the paper, "A Practical Method of Visualization of the Chambers of the Heart, the Pulmonary Artery, and the Great Blood Vessels in Man and Its Clinical Application," by Dr. George P. Robb, and Dr. Israel Steinberg, New York, N. Y.

Dr. Howard B. Sprague, Boston, Mass.—Certainly there is no question about the great potential value of this type of study because one immediately realizes in one's own experience, I am sure, cases in which such information would be of great value.

We have had such problems, particularly of syphilitic involvement of the great vessels and congenital abnormalities, in which this particular technique would have helped a great deal. It is a technique which is apparently safe, and that is the first thing we have to think about; and it has been tested on patients who have been severely ill.

I would like to congratulate the originator of this method and trust that many of our clinics will now go ahead and experiment with it.

Dr. William J. Kerr, San Francisco, Calif.—Mr. Chairman, I must apologize to you all and to the speaker. Because of the many details arising in connection with the meeting in our city, it was impossible to get back in time to hear this paper presented.

I have heard a good deal about this work, however, and have been tremendously interested in the possibilities the method offers for further study of the chambers of the heart and the dynamics of the circulation. I am sure it is going to be a very valuable method if it is safe to employ it in the study of a good many types of clinical conditions.

I regret that I cannot say more about it at this time.

Dr. Robb (closing).—As to the question of dosage, it varies roughly with the body weight. In normal persons 35 c.c. of the 70 per cent solution of diodrast is usually enough for visualization of the heart and the aorta. For pulmonary arteriography, 30 c.c. usually suffices because a lower concentration gives sufficient contrast in the lungs.

However, in patients who have thick chests, enlargement of the heart or aorta, or pulmonary enlargement, it has been necessary to increase the amount. The maximal dose has been 45 c.c.

Question from the floor.—At what rate?

Dr. Robb.—The injection should be completed in two seconds or less. Such rapidity is contrary to accepted clinical practice and was adapted only after cautious trial had proved that it was safe. Determinations of the arterial and venous blood pressure, and electrocardiograms and clinical observations made continuously during the injection and repeated afterward, have revealed no adverse effect upon the heart.

The rapid delivery of the diodrast into the superior vena cava is achieved by the forcible flushing of the peripheral vein with blood after the injection. The blood is withdrawn into the syringe before injection and, being lighter, rises to form a column above the diodrast.

Question from the floor.—What is the size of the needle you use?

Dr. Robb.—A 12 or 13 gauge needle one and one-half inches long is used in adults. It is advisable to test its location within the vein by the injection of normal saline solution. This is readily done since the needle is attached to a two-way stopcock before insertion into the vein.

Discussion of the paper, "Analysis of Results Following Sympathectomy for Peripheral Vascular Disease," by Dr. Géza de Takats, Chicago, Ill.

Dr. Frederick Leet Reichert, San Francisco, Calif.—I am indeed sorry that Dr. de Takats was not able to attend the meeting, but I have enjoyed giving his paper

and agree with him that interruption of the sympathetics to the extremities is of definite help in the treatment of peripheral circulatory disturbances.

Out here most of these patients are seen in the Outpatient Clinic of Stanford University Medical School, and, as the economic recession has been of such long standing, we have not been able to have them enter the hospital for operative removal of the sympathetics. In many instances we have resorted to interruption of the sympathetics with alcohol injections.

We prefer the operative removal of sympathetics for the upper extremity and, in many instances, the alcohol injection for the lower extremity.

Dr. de Takats has mentioned the importance of classification of the cases in determining the degree of structural involvement as a criterion for operation on the sympathetics and whether it will be successful.

Several years ago we performed a number of tests on these patients, but we soon learned that environmental temperature was important and that we could not tell whether there would be a good result unless the patient was in a cold environment. Since putting them in a cold environment is harmful, we have dispensed with many of the elaborate tests and depend upon the circulatory appearance of the extremity and the history in deciding what is to be done. In reality, it does not make very much difference to us now whether we classify the cases as Raynaud's disease, Buerger's disease, or arteriosclerosis, as our treatment is much the same.

We force fluids, have the patients stop tobacco, and teach them the importance of being in a warm environment. When they have learned these things, we may try venous hyperemia or passive vascular exercise, or we might suggest interruption of the sympathetic chain. The patient is told that by sympathetic interruption we are attempting to give him vasodilatation twenty-four hours of the day, and also that we are simply treating a symptom so that he must regulate his life accordingly.

I do feel with Dr. de Takats that we do not see the early phases of these conditions and perhaps if we make our patients realize the importance of the proper care of their legs, which have been carrying them around for many years, and if we, as physicians, realize that in patients over forty years of age it is more important to feel for the pulses in their feet rather than the radial pulse, we may be able to help these individuals a great deal without any surgical treatment.

Our results have been good in what Dr. de Takats calls reflex dystrophia and causalgia in painful amputation stumps, as well as the cold, spastic extremities that occasionally follow hemiplegias.

Dr. Winchell McK. Craig, Rochester, Minn.—I think Dr. Reichert has covered the subject very well. Also, he has brought out one matter that I think is important; namely, that the economic situation of the patient determines the method of treatment. I am very much interested in the results which he has been able to obtain in the outpatient department.

Discussion of the paper, "Skin Temperature Studies After Sympathectomy and Deafferentation," by Dr. Robert A. Phillips, Dr. James D. Hardy, and Dr. Joseph C. Hinsey, New York, N. Y.

Dr. Edgar V. Allen, Rochester, Minn.—A few months ago, when I was in New York, I had the opportunity of visiting Dr. Phillips' laboratory and discussing some of these problems with him.

The point which he makes, in brief, is that he has a method which he has worked out with Dr. Hardy and Dr. Hinsey whereby he may determine how much blood is shunted from a part, at least from the skin of that part, as a result of any procedure such as the intravenous injection of adrenalin.

You may know that sympathectomy for Raynaud's disease of the lower extremities results in cure in almost all instances. The results of the operation in cases

of Raynaud's disease of the upper extremities are much less satisfactory. When the neurosurgeon performs lumbar sympathectomy, he cuts the preganglionic fibers, because the ganglia which supply the lower extremities are distal to the lumbar ganglia, but when performing sympathectomy for Raynaud's disease of the hands he removes the ganglia which supply the upper extremities.

This led to an ingenious explanation for the difference of results in operations for Raynaud's disease of the upper extremities, namely, that the operation for the lower extremities, which was preganglionic, did not produce greatly increased sensitivity to adrenalin as did operation for the upper extremities, which was postganglionic.

The recurrence of color changes after cervicothoracic sympathectomy was supposedly due to increased sensitivity of arterioles to adrenalin. That gave us all very much hope that the same type of operation could be performed for Raynaud's disease of the upper extremities as was performed for the lower extremities, namely, preganglionic section, and such an operation was devised.

Unfortunately, that operation did not produce as good results as anticipated, and certainly not as good as those which follow lumbar sympathectomy for Raynaud's disease. Thus, the explanation mentioned in the preceding paragraph for the failure of the operation to relieve Raynaud's disease of the hands may be questioned seriously. I believe it probable that the explanation for the divergence of results of operation for Raynaud's disease of the hands and of the feet cannot be explained on the basis that one operation is postganglionic and the other is preganglionic. The work of Dr. Phillips and his associates may clarify the situation.

I would like to have Dr. Phillips answer this question: Is it true from his study that sympathectomy of the preganglionic fibers or postganglionic fibers does not cause an increase in the sensitivity of the arterioles to adrenalin?

Discussion of the paper, "The Isolation of Nicotine from Human Urine," by Dr. Irvine H. Page, Dr. O. M. Helmar, and Dr. Kenneth G. Kohlstaedt, Indianapolis, Ind.

Dr. A. W. Duryee, New York, N. Y.—I have just one little comment to make, namely, that this test gives us a good check on whether our patients with thromboangiitis obliterans have stopped smoking.

Dr. William J. Kerr, San Francisco, Calif.—I would like to ask whether those who chew tobacco have the same or an increased effect.

Dr. Edgar V. Allen, Rochester, Minn.—It would appear that Dr. Page's work is another link in the chain which condemns smoking as a harmful practice for human beings. We know that the inhalation of tobacco may cause sharp increases in blood pressure. We know, also, that the inhalation of tobacco smoke may cause sharp decreases in the surface temperature of the skin of the extremities, indicating vasoconstriction. We know, further, that the inhalation of tobacco smoke may cause visible vasoconstriction in the retina.

We all know that those of us who smoke are subjecting ourselves to a strong vasoconstrictive agent every time we smoke. Those of us who are sensitive to tobacco smoke get a more sharp physiologic response in these various ways than those who are not sensitive to smoke.

However, I should like to point out that it is a long jump to say that because a drug produces a physiologic effect, it is also capable of producing an organic one. For instance, although the inhalation of tobacco smoke causes a sharp decrease in the temperature of the skin of the extremities, so may the ingestion of a glass of cold water or the exposure of any part of the body to cold, and we hardly consider that these things are capable of producing organic changes.

However, there is some evidence, I think, that the use of tobacco is harmful in certain individuals with hypertension, and it certainly seems to be definitely harmful to individuals with thromboangiitis obliterans, because it appears to produce physiologic changes in the arteries by its vasoconstrictive effect, thus adding to the already diminished circulation to the lower extremities.

You may all have read or heard a recent statistical report by Dr. Raymond Pearl which gives a little more grave thought to the subject than I have indicated. If Dr. Pearl's statistics were reported correctly in the news magazines, he has shown that, other things being equal, the smoking of tobacco directly influences longevity. Those who do not smoke live longer than those who smoke slightly. Those who smoke heavily live less long than those who smoke slightly. In other words, there is a direct linear relation between the use of tobacco by smoking and the length of life.

Those of you who have been sitting here all day, smoking one cigarette after another, may go away with this thought in mind.

The work of Dr. Page and his associates is an important contribution to an understanding of physiologic and organic changes which may result from tobacco smoking.

Dr. Page (closing).—I had no intention of suggesting that cigarette smoking was either good, bad, or indifferent. I think, however, that now that we have methods available for studying this problem, it is worth the effort because, after all, if nicotine is excreted in the urine, it may be that a clearance of nicotine may be done to determine the way different people metabolize it.

As to whether chewing tobacco has the same effect as smoking, I should guess that it has. We in Indiana do not chew, so we do not know.

I forgot one thing which is of some interest, I think. We have not actually isolated crystals of nicotine from the blood, but we have separated extracts of blood which seem to contain nicotine. Thus apparently nicotine circulates as any other substance does. It is quite difficult for the body to destroy it, otherwise the liver would presumably have done so completely instead of allowing some to be excreted in the urine.

In Memoriam

John Wyckoff
1881-1937

John Wyckoff made an important place for himself in American medicine through the force of his character and the originality of his thought. He was a generous and stimulating teacher and a forthright and understanding administrator. In a few brief years he enhanced the position of his school, he assembled a staff of devoted and energetic associates, he made important scientific observations, and he made an impress on the leaders in education in medicine. And all of this he accomplished through the force of his commanding personality—uncompromising, scrupulously just, liberal, and sympathetic in temperament and in conviction. The passing of such a man leaves a void.

Wyckoff was born in the Madras presidency, in India. His education he obtained in the United States. He was a student for two years at Rutgers College, receiving an honorary M.A. in 1920. He was graduated with the degree of M.D. in 1907, from New York University and Bellevue Hospital Medical College. His association there with Doctor Hermann Biggs was important in turning his attention in the direction of the study of cardiac diseases (1909). A little later (1914 to 1915) he joined Doctor Hubert V. Guile in the conduct, under the auspices of the Social Service of the Bellevue Hospital, of the first cardiac clinic (1911) in the United States. This association was, in all likelihood, the determining episode in his life. After the War (he had accepted a commission in the United States Army in February, 1918) he rejoined Dr. Guile (1919) and in the same year he inherited this cardiac clinic. This clinic, under his guidance, became the model for all future enterprises of this nature. Here he demonstrated the variety and thoroughness of the services a cardiac clinic, and by inference, other clinics, can render. Here he carried on his chief scientific work. Here he indoctrinated a great many men in the method and object of medical research. This clinic was to the end, I think, his chief pride. Its creation, in the form he gave to it, was certainly his chief distinction.

The general situation of patients suffering from cardiac diseases was becoming (1915) the concern of several thoughtful physicians in New York, and the result was The Association for the Prevention and Relief of Heart Disease, subsequently The New York Heart Association. Wyckoff became a member of this organization in 1920, being a member also of The Association of Cardiac Clinics, organized in February, 1917, and joined to The Association for the Prevention and Relief of Heart Disease in April, 1923. In both organizations he was active and soon became a leading spirit. In 1923 (November 26), Wyckoff became

John Wyckoff

Chairman of The Association of Cardiac Clinics, succeeding William P. St. Lawrence, and in 1926 (March 18), Chairman of The New York Heart Committee, a position which he held until January 1, 1933. In 1935 and 1936 he was President of The American Heart Association.

Wyckoff was the first, so far as I am aware, who made public use of the realization, growing for several years, that "heart disease" was not a unit. He devised for use in his clinic a threefold form of classification and introduced it in his clinic in 1919. The main heads he proposed were: (1) anatomic, (2) functional, and (3) etiological. Under etiology he provided for the entry of cases resulting from syphilis, rheumatic fever, and senility, and also other acute infections, alcoholism, and "others." In preparing its clinical charts* during 1920 and 1921, a similar plan, independently developed, was adopted by The Association for the Prevention and Relief of Heart Disease.

In this clinic he made the first modern study, utilizing the charts just mentioned, of the incidence† of the various cardiac diseases. To his conviction that this method of accumulating information is useful he gave expression in at least four publications. With this technique he proceeded over a period of years and in association with a succession of colleagues to publish papers on a number of aspects of diseases of the heart, on rheumatic fever, on arteriosclerosis or senescence, on pharmacology, and on treatment.‡ In the brief space available it is impossible to describe his various researches. But it is important in understanding the range and breadth of his insight to quote his remarks on arteriosclerosis: "Many of the questions which we wish to answer could be answered today if the thousands of careful observations made in the various clinics in this city on patients having arteriosclerosis had been collected in a coordinated and uniform way, with the use of definite criteria, and if they had been placed upon a chart which would make them available for statistical study."

"It is my belief that the final answers to most of these questions will come from the careful study of patients in ambulatory clinics over long periods of time, where these patients are not only carefully studied, but where accurate and uniform data are obtained by every available method, and, after being selected, scientifically analyzed."

"Physicians often marvel at the time and patience which a laboratory investigator expends in the development of a proper laboratory technique. Our work, that is, properly coordinated clinical and labora-

*These were reproduced in "The Journal of the American Medical Association" in 1922 (78: 1559).

†Wyckoff and Lingg: Statistical Studies Bearing on Problems in the Classification of Heart Diseases. II. Etiology in Organic Heart Disease. AM. HEART J. 1: 446, 1926.

‡References to these papers are given in "John Wyckoff: 1881-1937." A. E. Cohn: Bull. Inst. Hist. Med. 6: 835, 1938.

tory investigation in chronic disease, demands a technique which is surely as difficult to perfect and the development of which takes years.''*

In the last years of his life, Wyckoff's energies were devoted to problems of education—the selection of students, the construction of the curriculum, the place of medical education in the scheme of things. His approach to the solution of all these matters was as free of preconceptions, as free of predetermining prejudice, as the desire to have it free could make it. If the best students were to be admitted to the schools, they must necessarily be those with the highest scholastic attainments. He found, on analysis, that men who had done best in college made the best medical students. The members that fell by the wayside, in his school, became fewer after scholarship became the chief criterion for admission. It was transparently clear that he valued men for their eagerness to render service, in practice or in teaching, and for their ability to attain high levels of intellectual performance. Under these circumstances he gathered about himself a group of men distinguished for their energy, their disinterestedness, their devotion to his elevated views. The purity of his own ambitions elicited an extraordinary response; men followed where he led and gave him unstinted personal loyalty.

The profession of medicine in the difficult years that lie ahead can ill afford his loss. His open-eyed way of meeting experience had prepared him to lead in ways calculated to understand and to do justice to the interests of the various elements that serve to make up the medical community. He would have known how to adjust the services physicians in their various callings could render to the requirements of men in general. He would have known how to attain the objects at issue without permitting the adjustment to descend to the level of a wrangle. He would have helped to see to it that the complex interdigitating interests became suitably adjusted. He was an administrator who knew that more was wanted in a forward-looking world than to provide merely for the technique of successful manipulation.

It is well not to permit the memory of men like Wyckoff to fade. Their influence, their elevated enterprise, their moral persuasiveness serve to commit men to the most sympathetic service in the interests of society. The realization that Wyckoff had these qualities caused his contemporaries to hold him in high esteem and to give him those opportunities which he used in so distinguished a manner.

Alfred E. Cohn.

*A Consideration of the Possibility of the Prevention of Arteriosclerotic Heart Disease. Tr. Am. College Physicians, Philadelphia 51: 95, 1929.

Department of Reviews and Abstracts

Selected Abstracts

Prognosestudier ved kroniske Hjertelidelser med Henblik pae Elektrokardiogrammernes prognostiske Betydning (The Prognosis in Chronic Heart Disease With Special Reference to the Prognostic Significance of the Electrocardiogram)

By Henning Aastrup, Copenhagen, Denmark

This thesis. written under the direction of Professor Erik Warburg, is an analysis of the cardiologic experience in the Second Division of the Municipal Hospital of Copenhagen between 1924 and 1928. It is a study of 797 patients who were hospitalized and had electrocardiograms, particularly with reference to their status after six to ten years.

The electrocardiographic literature is extensively reviewed. Willius' work is reviewed in detail and criticized. Objection is raised to the lack of information regarding the state of compensation of the patients and it is suggested that Willius' material consists of cases in which the disease was more advanced than in those of other authors. Willius traced only 70 to 80 per cent of his patients. This defect influences prognostic studies unfavorably, as shown by the author's own studies. The exact periods over which Willius' patients have been followed are not indicated. But in spite of these defects the author accepts Willius' conclusion that many electrocardiographic, especially T-wave, changes may be of important prognostic importance in cardiac patients, though Hamman, who examined patients with less advanced heart disease, considered Willius' conclusions much exaggerated.

Other studies reviewed in detail include the important work by Deindl (Arch. f. klin. Med. 178: 425, 1936). The review is arranged under the following headings: Negative T_1 and T_2; negative T_1 and left axis deviation; low and isoelectric T_1 and T_2; complete and incomplete bundle branch block; bundle branch block with short conduction time; negative T_3; negative and positive T_3 with left axis deviation; complete inversion of Lead III; negative T_3 with right axis deviation; low voltage; changes seen in coronary occlusion; deep Q_3; M- and W-shaped QRS complexes in Lead II; the second positive peak in QRS_3; slurring of the terminal limb of the R-wave in all leads; evolutive changes of the QRS complexes and the normal electrocardiogram.

The study of the literature shows that certain electrocardiographic changes are associated with a relatively high mortality within a relatively brief time. But opinions are divided as to the actual prognostic value of these changes, though they have recently been studied in much detail and in relation to their clinical associations. No electrocardiographic sign has absolute prognostic value. (It seems that denial of the prognostic value of the electrocardiogram is based upon excessive demands. Few clinical signs determine in themselves the prognosis, but when properly interpreted they aid in its formation.)

The contrasting views regarding auricular fibrillation in relation to the prognosis in general, and congestive failure in particular, are sharply drawn. Certainly the prognosis is worse if the ventricular rate is fast and cannot be controlled, probably

also when the ventricular complexes are abnormal, in the presence of extrasystoles, and especially in persons below the age of 20 years. The literature does not show whether the prognosis is better in arteriosclerotic or in rheumatic heart disease.

Then follows an analysis of the author's material. Nearly all the electrocardiograms were taken by Dr. Warburg personally. All terms are carefully defined. The effect of digitalis on the electrocardiogram is discussed, with stress on the prevailing effect on T_3 and T_2.

SYPHILITIC HEART DISEASE

Thirteen per cent of the patients had syphilis. In the general hospital population at the same time the incidence was 9 per cent. A diastolic murmur was heard in all cases in which autopsy later revealed the presence of aortic regurgitation. The diagnosis of syphilitic aortitis is uncertain clinically, though certain anatomically. The author shares the prevailing scepticism regarding syphilitic myocarditis; diffuse syphilitic involvement of the myocardium is very rare. He questions whether syphilis predisposes to the myocardial changes which so often occur in cardiovascular syphilis. He finds that in 80 per cent of cases of cardiovascular syphilis the serologic tests are positive. He stresses the danger of mistaking aortic regurgitation of other origin for that of syphilis, especially if the serologic tests are positive and the causative infection has been latent. Syphilitic aortic regurgitation is rare in patients under 30 years of age.

In about 4 per cent of all autopsies cardiovascular syphilis is present, and among older patients about 75 per cent with the organic changes of syphilis will show syphilitic changes in the cardiovascular system. This incidence can almost certainly be lowered by early and rational treatment, though this conclusion cannot be drawn from the author's own material. Clinically, cardiovascular syphilis occurs in about 25 per cent of persons suffering from late syphilis. Five to 20 per cent of patients with organic heart disease have cardiovascular syphilis. Among cases of aortic regurgitation the incidence of syphilis is high, varying from 30 to 70 per cent, according to how the material is selected. The author's figures and those in the literature agree on these points.

In his pathologic studies he finds that syphilitic aortitis was in no case the sole cause of cardiac hypertrophy. Cardiovascular syphilis was frequently associated with other cardiovascular disease, especially arteriosclerosis, and he discusses whether syphilis predisposes to arteriosclerosis or whether the coincidence is a sign of an inferior vascular system. (There is no proof that this coincidence is more than accidental.)

In syphilis, angina pectoris occurs often at rest, and its prognosis is considered worse in syphilis than in hypertension. He fails to find evidence that syphilis predisposes to hypertension. The coincidence of cerebrospinal and cardiovascular syphilis is 20 to 30 per cent. In 14 per cent of the author's cases there was a rheumatic background.

Of 27 cases of aortic regurgitation, death was caused by heart disease in 25. Sudden death is more common in syphilitic than in rheumatic aortic regurgitation. From a pathologic point of view aneurysms are the direct cause of death in 25 to 30 per cent of those who have them; clinically, the incidence is higher. Uncomplicated syphilitic aortitis is rarely fatal.

The average duration of life in syphilitic aortic regurgitation was three years from the onset of symptoms, but the value of this figure is impaired by the wide spread of the duration, viz., from one month to twelve years. Life is definitely prolonged by adequate treatment.

No electrocardiographic change is pathognomonic of syphilis. Auricular fibrillation occurs in about 5 per cent of the cases and is probably due to some con-

comitant factor other than syphilis. Bundle branch block has a very bad prognosis in syphilis. In 20 cases the T-waves were inverted, and in 4 of these this change preceded other signs of bad prognosis and was thus of real value. In general, the prognosis was bad in cardiovascular syphilis, though worse if the T-waves were negative than if the electrocardiogram was quite or almost normal. Both diagnosis and prognosis were often obscured by coincidental arteriosclerosis. In aneurysm and syphilitic aortitis the cardiac findings, including the electrocardiogram, are not of interest until the disease has extended to the coronary orifices or the aortic valves.

RHEUMATIC HEART DISEASE

In 223 (28 per cent) of the cases there was evidence of rheumatic infection, past or present. Aortic regurgitation, aortic stenosis, and mitral stenosis are the only lesions which can be diagnosed with certainty. It is difficult to determine whether old calcified valves are the result of a chronic infection with secondary calcification or of pure arteriosclerosis. In recent lesions the larger verrucous processes may be caused by recurrent rheumatic endocarditis, simple thrombi, or subacute bacterial endocarditis, and the smaller ones by recurrent rheumatic endocarditis, so-called terminal endocarditis, or small aseptic thrombi. After an extensive review of the literature he leans to the view that old stenosing lesions of the aortic valve (Mönckeberg) are as a rule primarily inflammatory with secondary calcification. Mitral stenosis was diagnosed only in the presence of the typical murmur. Neither clinically nor anatomically was it possible to differentiate between mitral stenosis and mitral stenosis and regurgitation. In spite of Dressler and Fischer's work, no effort was made to diagnose lesions in the right side of the heart (most of the diagnoses were made before 1929, however). A systolic murmur at the apex is a quite reliable sign of mitral regurgitation, but it has been present when the valves were normal, and absent when they were diseased. Mitral regurgitation was not the cause of death in any of the author's cases. However, some modern authors consider these views too extreme. The typical murmur of mitral stenosis the author found to be a constant and pathognomonic sign of the lesion. Mitral stenosis does not develop diagnostic signs until three to six years after the initial infection. Rheumatic aortic lesions almost always show signs of stenosis. Flint's murmur is rarely accompanied by a thrill and the second sound is never split. It was found in 7 of 19 cases of syphilitic aortic regurgitation, in none of which was mitral stenosis present at autopsy. While it contains nothing new, this is an excellent discussion of the criteria for diagnosis and the accuracy with which valvular lesions can be diagnosed. The strict criteria resulted in a higher incidence of combined mitral and aortic lesions in the pathologic than in the clinical analysis. Rheumatic valvular defects were diagnosed in 131 cases, in 127 of them, clinically; in 4 the diagnosis was missed clinically for good and sufficient reason. Without reserve the author seems to accept symphysis pericardii as rheumatic in nature. Sixty-nine per cent of the patients had mitral stenosis, 17 per cent mitral stenosis and aortic lesions, 14 per cent aortic lesions (15 regurgitation and 4 stenosis); 61 per cent were between 20 and 50 years of age, 20 per cent were past 50, and 19 per cent were below 20 years of age. Aortic regurgitation was rare in the young. Women prevailed among those having mitral lesions (69 to 43) and men among those with aortic lesions (18 to 1). Sixty-three and four-tenths per cent gave a history of polyarthritis, 5.3 per cent of chorea, and 31 per cent gave no rheumatic history. The average age at the first attack of rheumatic fever was 17 years; among those under 20 years of age it was 11, and among those above 50 it was 25. Pulmonary complications were frequent; 47.6 per cent presented them at the time of the first electrocardiographic examination. Respiratory infections were commonly the cause of heart failure. Cardiac asthma was more common in rheumatic heart disease than is generally assumed. Among 84 patients

with valvular disease who were followed till they died, 46 showed signs of embolism at one time or another, but many who did not die when embolism occurred lived for several years afterwards. Most of the emboli which were diagnosed clinically occurred in cases of auricular fibrillation. Angina pectoris occurred five times with aortic lesions, never with mitral lesions. Seven out of 90 patients with mitral stenosis had a systolic blood pressure of 160 or more, and all of these were more than 45 years of age. The same was true in 2 of 18 cases of mitral stenosis and aortic lesions, in 1 of 4 cases of aortic stenosis, and in 5 of 15 cases of aortic regurgitation. Hypertension did not add to the gravity of the prognosis.

Ninety per cent of the patients with rheumatic heart disease died from their heart disease, a great many of them with some terminal infection (bacterial endocarditis, rheumatic infection, colds, etc.). Subacute bacterial endocarditis was especially common in aortic lesions in men. Two patients with aortic stenosis died suddenly. All of these findings are discussed in the light of extensive collections of data from the literature.

In 43 patients dying from rheumatic heart disease the age at the time of the first rheumatic infection was known. On an average they lived for twenty-five years. The average age at death in 50 cases of mitral stenosis was 42.7, in 18 cases of mitral stenosis and aortic lesions 44.7, in 16 cases of aortic lesions 55 years, and in the whole group of 84 cases 45.5 years. Comparing his experience with that of others, he points out that the relatively low age in the series reported by DeGraff and Lingg (33 years) may be due to the facts that the patients as a whole were relatively young, and that only 73.3 per cent of the 1633 patients had been traced (the author traced all of his but one). The older the patient is at the time of his first attack, the shorter his life expectancy. This may be because this series does not include the children who died within a few years of their initial infection. The number of attacks of rheumatic infection and the type of valvular lesion do not seem to affect the prognosis.

Auricular fibrillation occurred in 71 per cent of the patients who were followed till they died. It occurred late in the course of the disease. In the author's entire series it was as common in aortic as in mitral lesions, but among those who died it more frequently accompanied mitral lesions. Auricular fibrillation and subacute bacterial endocarditis coincided very rarely. Auricular fibrillation was rare in youth. It was relatively often associated with changes in the ventricular complexes in the cases of aortic regurgitation, but with mitral stenosis such changes (except right axis deviation with or without negative T_3) were rare.

The cases with normal rhythm were analyzed in detail but offered nothing of special interest.

Of 56 patients with rheumatic heart disease and auricular fibrillation, 84 per cent died from cardiovascular complications after an average of thirty months. When all of these patients have died, they will have survived, on an average, three to four years. However, in any statistical study of this kind the result will depend upon the nature of the material, especially with respect to how many patients below the age of 20 years it includes, and the number of cases of terminal and "catastrophic" auricular fibrillation. This again will depend upon how closely the patients have been followed in the terminal stages. The author next excludes the patients with a very unfavorable prognosis, then adds to the lifetime of the others the period between the discovery of the auricular fibrillation and the first electrocardiogram, and then finds that the average period of survival for 42 patients was close to five years. Sixteen of these died within three years of the discovery of auricular fibrillation, but only 5 of them from congestive failure; the others died from embolism and other dramatic events. This experience led the author to a less pessimistic view on the prognosis of auricular fibrillation.

In decompensated patients the prognosis was determined by the cause of the congestion; if this was transitory, as in the case of acute respiratory infections, the prognosis might be quite good. Patients with auricular fibrillation, right axis deviation, and a negative T_3 died sooner than those with normal ventricular complexes. Cases of rheumatic heart disease taken as a whole, a negative T_1, with or without other T-wave changes and incomplete bundle branch block, gave a bad prognosis, for all the patients with these lesions had died, while almost all of those with normal electrocardiograms survived. This distinction was less marked among the very old patients. The prognosis when the T-waves were isoelectric was somewhat better than when they were negative. Most of those patients with negative and isoelectric T_1 waves who died within three years presented other signs of a bad prognosis also. Patients with right axis deviation and a large P_2 showed a tendency to auricular fibrillation and had a greater death rate than those with other minor abnormalities. The prognosis of negative T_3 was worse if right axis deviation was also present; in most of the patients who died there were also other signs of a bad prognosis. Likewise, it was worse if T_2 also was negative, but a definite statement on this point was difficult because in many of the patients this change might have been produced by digitalis. Of the group of patients with rheumatic valvular disease and T-wave changes but without complete A-V block or auricular fibrillation, 71 per cent died, on an average, twenty-eight months after they were first observed. However, the author believes that the prognosis in cases in which there were T-wave changes would be better if those cases were excluded in which, on clinical grounds alone, the prognosis was bad. Again he mentions that Willius' unfavorable experience with T-wave changes could be explained by a high incidence of decompensation cases. Both Willius and others found that the various T-wave changes are not in themselves incompatible with several years of life. They often precede clinical signs of a bad prognosis, especially in chronic, rheumatic, aortic lesions. On the whole, he decides, the prognosis in cases in which there are T-wave changes is better than is generally assumed, though not as good as when the electrocardiogram is normal. The electrocardiogram is of real prognostic value. Right axis deviation with negative T_3 had about the same prognostic value as left axis deviation with negative T_1.

HYPERTENSION, AND DEGENERATIVE HEART DISEASE

If these patients develop congestive failure, tests of renal function are of less value. Also, percussion is of limited value in determining the size of the heart. The author seems to use the term "degenerative heart disease" in a more comprehensive sense than do most American authors.

Of 154 fatal cases of essential hypertension, 64 per cent of the patients died from heart disease (50 per cent of this number from congestive failure, 25 per cent suddenly), 17 per cent from apoplexy, 4 per cent from uremia, and 16 per cent from other noncardiovascular causes. These figures compare interestingly with those of other investigators, especially those of Bell and Clawson. The low incidence of uremia is striking, but is explained by the rigid exclusion of nephritic hypertension from the series.

The apical systolic murmur, so common in hypertension, was studied especially. It was found in 22 patients who later came to autopsy. In 4 the valves were definitely deformed, 7 had slight changes in the form of calcification of the bases of the valves, and 11 were entirely without valvular changes. Most of the hearts were hypertrophied but there was no proportion between the degree of hypertrophy and the degree of hypertension. Most of the patients with hypertension who died from congestive failure had marked coronary sclerosis and myofibrosis. Definite myomalacia was found in 15 of 94 patients who came to autopsy.

There were 69 cases of angina pectoris, and in 32 (including 2 in women) there was coronary thrombosis, fresh or old. Fourteen had diabetes (this statement was not amplified by further diagnostic detail).

Of the 19 patients with coronary thrombosis, 16 had died. Eleven could date their first attack. Five died within a month, and on an average (including 3 survivors) they had survived for two years. The survivors had survived nine, eight, and six and one-half years, respectively. The average period of survival in any such series depends on how many patients are included who died immediately or soon after an attack. It is naturally longer if it is limited to patients who have survived for at least two months. First attacks of coronary occlusion are rarely fatal. During the acute stage the prognosis is best evaluated by considering the general state of the patient, the droop in blood pressure, and the degree of fever. Paroxysmal ventricular tachycardia and arborization block he found to be grave complications. There was no marked difference in prognosis between anterior and posterior occlusions. He did not say whether a rapid return of the electrocardiogram to normal may be considered a favorable sign.

Of 50 patients with angina pectoris, 41 had died, 34 of them from heart disease (4 in status anginosus, 2 of apoplexy). Thirty-seven about whom information was available had survived from two months to thirteen years, on an average about four and one-half years. The 9 who survived had had the disease, on an average, ten years. Those with hypertension had all died. Only 3 of the 50 had quite normal electrocardiograms, rather a small number. None had auricular fibrillation. Twenty-two had a negative T_1; 86 per cent of these had died from cardiovascular disease after an average period of twenty-five months. Of the 3 with normal electrocardiograms, 2 were still alive. Thus the normal electrocardiogram seemed to offer a better prognosis. The prognostic value of the electrocardiogram was definitely less above the age of 63 years. Below that age the value was less in angina pectoris than in other conditions, because these patients are subject to sudden changes for the worse, especially coronary occlusion. On the other hand, in angina pectoris the electrocardiographic changes were relatively often the only sign, apart from the pain, which indicated a change in prognosis.

In 154 fatal cases of hypertension the largest number of patients died between the ages of 60 and 70 years; only 8 per cent were below 50, and 33 per cent were above 70 years of age.

The result of prognostic studies in hypertension depends upon whether the group chosen consists of ambulatory or hospital patients. If the symptoms are severe enough to demand hospitalization, life expectancy is generally limited. In all groups, men showed the highest death rate. Schwensen (Ugesk. f. laeger 98: 1264, 1936) followed 159 (57 of whom were women) Danish hospital patients with hypertension. After seven and one-half years the death rate was 74 per cent for the men and 50 per cent for the women. The prognosis for the men seemed to be independent of the height of the blood pressure. For the women there was a definite relation between the two, for among 21 with a systolic blood pressure above 225 the death rate was 71 per cent, among 39 with systolic pressures of 200 to 225 it was 44 per cent, and among 22 with systolic pressures between 170 and 199 it was 32 per cent. Roslin (Acta med. Scandinav. 83: 41, 1934), for 8 years, followed 102 patients receiving sickness benefits for essential hypertension. Seventy-two were still alive at the end of the period. Of 205 with essential hypertension and cardiac symptoms 53 per cent were alive after eight years.

Of Aastrup's 186 patients, 27 per cent had normal electrocardiograms, 19 per cent auricular fibrillation, 2 per cent complete A-V block, 11 per cent left axis deviation with negative T_1; 20 per cent a negative T_1 with or without other T-wave changes, 2 per cent negative T_2 and T_3, and 7 per cent left axis deviation.

Of 36 patients with auricular fibrillation and hypertension, 78 per cent died of cardiovascular causes after an average of thirty months, and 8 per cent lived after an average of eight years. Of 26 patients with degenerative heart disease with auricular fibrillation but without hypertension 58 per cent died after an average of nineteen months. Sixty-nine per cent of all the patients with auricular fibrillation died from cardiovascular causes after an average period of eighteen months, and 19 per cent survived for an average period of seven years. These figures correspond closely with those for mitral stenosis. But three-fifths of the patients with hypertension and degenerative heart disease were above the age of 63 years, whereas only one-twelfth of those with mitral stenosis had passed this age. Considering only the patients below the age of 63 years, the average period of survival (about four years) was about the same for degenerative and mitral heart disease. Nearly all the patients less than 63 years old who had died in less than three years died from special complications, or there was evidence that the arrhythmia had existed for a considerable time before the first electrocardiogram was taken. In this group also, therefore, the average duration of auricular fibrillation is considerably above four to five years when the patients with special complications are excluded. The "catastrophic" type of auricular fibrillation which was noted in mitral stenosis was not seen in cases of hypertensive or degenerative heart disease. The course of the auricular fibrillation was more favorable when the ventricular complexes were normal. One patient with auricular fibrillation had no other signs of heart disease and was considered as belonging to the group in which auricular fibrillation is without prognostic significance.

A relatively large number of patients with hypertension, regular rhythm, and inverted T-waves died within a relatively short time, but among those with normal electrocardiograms few died from heart disease during the period of observation. T-wave changes frequently preceded other signs of an unfavorable prognosis. Of those with normal electrocardiograms who died, a disproportionate number were above 63 years of age, and consequently the prognostic value of the electrocardiogram was greatest below that age. Among the cases with T-wave changes, the addition of left axis deviation did not seem to aggravate the prognosis.

Among 27 patients with hypertension and late syphilis the death rate was about the same as among those with hypertension and no syphilis. Among the adults with cardiac symptoms and rheumatic history but without certain signs of valvular affections a relatively large number had hypertension, including all of those with a negative T_1, and most of those with auricular fibrillation.

Thirty-nine patients were observed during their first attack of rheumatic fever. During the first five years none of them died. During the second five years, 2 died from heart disease following another attack of carditis or from ulcerative endocarditis.

One patient had bundle branch block and a short A-V conduction time. The course was favorable as long as the patient was observed, and the author takes a view of this condition which is somewhat more optimistic than that of Wilson.

Finally, the author concludes that in general his findings conform with the prevailing views expressed in the literature. He emphasizes the part played by respiratory infections in precipitating congestive failure. When the T-waves changed, the heart generally deteriorated, though there was no absolute parallelism between electrocardiographic changes and the progress of chronic heart disease.

Certain T-wave changes have ominous significance, varying with the form of heart disease. The prognostic value is greatest between the ages of 20 and 63 years. If electrocardiograms were taken more commonly in the routine follow-up studies of patients with heart disease their prognostic value would unquestionably be enhanced. Especially, if patients could be followed through to the end one would learn much of the prognosis at the onset of the changes.

Above the age of 63 years the prognostic value of the electrocardiogram is not so great. Many old persons will long survive with marked changes, and many have normal electrocardiograms shortly before they die. Probably the cardiac changes which produce abnormalities of the electrocardiogram develop so slowly in old age that the heart has a chance to compensate for them, while, on the other hand, even a relatively well-preserved myocardium in old persons has but a limited reserve which is easily exceeded in case of sickness.

Below the age of 20 years most cardiac patients have rheumatic heart disease, and death is caused by acute carditis; the prognosis is then determined by its occurrence.

Among cardiac patients between the ages of 20 and 63 years, with normal electrocardiograms, the course was on the whole favorable during the period of observation, except among those with syphilitic aortic regurgitation, and even here there were some irregularities of the R-waves in those who died. T-wave changes generally mean that the process is more advanced and that the period of survival is limited, but, on the other hand, the author believes that these changes occur earlier than is generally assumed. Between the upright and the negative, stand the isoelectric T-waves; their significance depends upon the rate at which the wave is changing. The prognosis of inverted T-waves in women with hypertension is best.

Functional tests the author considers of limited value because they are so often affected by extraneous factors.

Another reason why the electrocardiogram has so great a prognostic value is that most cardiac patients die from their heart disease, and usually from congestive failure. Among the patients who died from increasing failure and in the group in which the largest number of patients had died from congestive failure the course of the disease corresponded best with the prognosis indicated by the electrocardiogram.

The operative death rate is greater among patients with abnormal than with normal electrocardiograms. The prognosis is about the same in complete and in incomplete heart block; these usually, but not always, occur during the last stages of chronic heart disease. If the clinical condition does not change in a year or two, the prognosis is much improved. Arborization block carries about the same prognosis as bundle branch block. In coronary occlusion these changes are a very bad sign. Intraventricular block with a wide S_1 is evaluated differently by various authors; some consider it of no consequence, and others think that it is as serious as other forms of bundle branch block; certainly it seems to be of no consequence in younger persons without marked cardiac symptoms. Low voltage is of no consequence apart from heart disease, but in congestive failure it is a serious sign if it does not change on treatment. A deep Q_3 is commonest in angina pectoris and is then usually associated with other changes. Many patients with a deep Q_3 die suddenly, but the average duration of life of patients with this complication has not been determined. When it is found in healthy persons the heart usually lies in a transverse position.

The significance of inversion of T_2 and T_3 is similar to that of inversion of T_1, but is less serious. An isoelectric T_2 is of no consequence. Left axis deviation with T_3 higher than T_1 is found in real heart disease, and if in such cases S_2 is deep and T_1 low or isoelectric the heart is almost certainly diseased, but for a proper interpretation of these tracings it is necessary to know the position of the heart, preferably from roentgenologic examination. Complete inversion of the complexes in Lead III is seen mostly in obesity.

As his main conclusion the author finds that the greatest prognostic value of the electrocardiogram is in cases of chronic heart disease in which definite clinical signs of prognostic value have not appeared or are difficult to interpret.

Dr. Aastrup's book is an ambitious piece of work, beautifully done. Throughout, the author restrains himself to such conclusions as are warranted by his as-

sembled facts. He has been fortunate in combining with indefatigable industry and his own common sense the counsel of one of the most clear-thinking cardiologists in Europe. Unfortunately the book will probably never reach as wide a circle of readers as it deserves, for it is published as a thesis in a very limited edition in Danish.

JULIUS JENSEN.

Paff, George H., and Johnson, J. Raymond: The Behavior of the Embryonic Heart in Solutions of Ouabain. Am. J. Physiol. 122: 753, 1938.

The forty-eight-hour embryonic chick heart exposed to a 1:300,000 dilution of ouabain undergoes A-V block, ventricular stoppage, and finally sino-atrial stoppage. The block is most constant as to time of appearance. Higher dilutions or lower temperature greatly delays these effects. These reactions are reversible since a quiescent heart can be revived by washing with Tyrode's solution. The cause of block apparently lies primarily in depression of irritability.

AUTHOR.

Cossio, P., and Martinez, F.: Graphic Registration of the Percussion Sound of the Chest. Rev. argent. de cardiol. 5: 1, 1938.

The percussion sounds recorded by means of a microphone (30 cm. from the chest wall) showed characteristics allowing recognition as regards sonority, dullness, and tympanism. The records show that both lung resonance and hepatic dullness are due (1) to vibrations originated by the striking finger and (2) to the movement of chest wall and underlying structures interfering with each other. In the case of the normal lung resonance the former only last for a brief initial period and the latter integrate the whole duration (0.4 to 0.5 second) of the acoustic phenomenon, the last portions of the vibratory phenomenon being formed only by them. In the case of hepatic dullness, the finger and chest wall vibrations predominated, but there were also present some lung vibrations due to the pleximeterlike action of ribs.

In six cases the heart area was traced by percussion with the sounds recorded as described, and the results were compared a posteriori with the x-ray pictures. The following findings were made:

The superior limit of the liver was marked too low in front of the mid-axillary line but sometimes at the right heights are even higher. Right of the sternum there was no change in resonance even though the right auricle surpassed its border in 1.5 to 3 cm.; only in cases of heart enlargement to the right can a lessened resonance be found to the right of the sternum. The left border of the heart at the level of the fourth or fifth interspace was marked from 1 to 2 cm. toward the left from the true place. Coincidence or error in the other direction was exceptional.

On the left parasternal line, diminution of resonance only occurs below the superior part of the left heart border and only coincides when this portion is formed by the pulmonary conus due to enlargement of the right ventricle.

The differences between the limits as marked by percussion and the real situation are explained by the deep location of the organs and also by the curvature and regional peculiarities of the chest wall.

AUTHOR.

Bean, William Bennett: Infarction of the Heart. II. Symptomatology of Acute Attack. Ann. Int. Med. 11: 2086, 1938.

The incidence of cases of cardiac infarction coming to autopsy increased fourfold in the later of two fifteen-year periods investigated. Of 300 patients on whom autopsy was done, 114 died within six weeks of the initial infarction; 75 patients had multiple lesions and survived more than six weeks; old scars were found in 111 cases.

Correct diagnosis was rare in the absence of pain. Mistaken diagnosis was usually confused by the symptom of pain. One-third of the cases showed signs of congestive failure before acute infarction. A prodromal period of pain occurred in 16 per cent of acute attacks. Pain and congestive failure occurred together in many cases. Dyspnea was the most frequent symptom and where associated with a sense of constriction merged into the ill-defined domain of pain. No constant morphologic finding could account for the vagaries of pain, its presence or absence, its location and radiation. Some evidence indicated it to be conditioned by individual differences, a cerebral rather than cardiac function. In acute cases without pain the onset was frequently characterized by sudden accession of failure, less often by central nervous symptoms (syncope, weakness). Tachycardia, enlarged heart, feeble heart sounds, and arrhythmias were frequently encountered. Pericardial friction rubs were heard in 41 per cent of cases with acute pericarditis. The arterial blood pressure was found to remain elevated in a large number of cases, though the majority showed declining levels. Fever and leucocytosis, although usually present, were absent in an appreciable number of cases.

Electrocardiographic studies revealed prolonged P-R interval in 25 per cent and prolonged QRS intervals in 46 per cent of all cases. These conduction defects were almost twice as common in predominantly right artery involvement as in left. The diagnosis of anterior infarction was usually correct, but one-fifth of those diagnosed posterior infarcts were wrongly localized. A large Q-apex invariably indicated posterior location and absent Q-apex invariably indicated anterior infarction.

AUTHOR.

Bean, William Bennett: Infarction of the Heart. III. Clinical Course and Morphological Findings. Ann. Int. Med. 12: 71, 1938.

No specific prognostic gauge was found to be valid in an individual case. Congestive failure and shock followed in more than half of the acute attacks. Enlarged liver and jaundice were observed in a small proportion of cases. Peripheral embolism was found most frequently in the second, third, and fourth weeks. Many incidents considered clinically to be embolic were found to depend on local vascular faults. Causes of death were investigated, and the predisposing influence of syncopal attacks was noted in cases of sudden death. Seasonal variation of death was in part influenced by seasonal fluctuation in incidence of acute attacks.

The left coronary tree was seriously involved in 84 per cent of cases, the right in 21 per cent. Nine cases of ectopic infarction appeared. Twenty per cent of the infarcts followed arterial narrowing without thrombosis. In four cases no arterial damage was detected. Eight cases of coronary anomalies were found, one with a small coronary aneurysm. The heart was enlarged in 83 per cent of the cases. The largest hearts were found in hypertensives. Ventricular mural thrombi were found in nearly half the cases; emboli were detected twice as frequently in instances of right ventricular thrombi as in cases of mural thrombosis of the left ventricle. Some thrombi were present three years after acute infarction. Embolism was most frequent when the thrombus was attached to the interventricular septum. Ventricular aneurysm was found in 10 per cent of the cases and appeared as early as the seventeenth day after infarction. There were three cases of extensive calcification of scars. Spontaneous rupture of the ventricle occurred in seventeen cases. One survived rupture eight days. In one case an aneurysm was ruptured by a needle. Four cases of coronary embolism from friable valvular vegetations were found, and there was one probable case in addition. There were two auricular infarcts. Pericarditis was found in 32 per cent of the cases and an effusion of 50 c.c. or more, in 15 per cent. Hydrothorax was frequent, and in many cases was greater on the right.

AUTHOR.

Kinsella, Ralph A., and Muether, R. O.: Experimental Streptococcic Endocarditis. Arch. Int. Med. 62: 247, 1938.

Seventeen dogs were subjected to operation whereby the mitral valve or the chordae tendineae were cut. All these animals were then fed with living cultures of nonhemolytic streptococci, either mixed with food or by stomach tube. Ten of the animals became sick, displayed positive results of blood culture, and died. At autopsy these infected animals had bacterial endocarditis. The bacteria in the vegetations were determined to be identical with those that had been fed to the animals.

Streptococcic endocarditis can be produced in dogs with injured cardiac valves by feeding them streptococci.

The fact is thus established that bacteria entering the animal body through the mouth may become implanted on an injured area within the body. The exact route which these bacteria follow is not determined.

AUTHOR.

Taussig, Helen B., Harvey, A. McGehee, and Follis, Richard H., Jr.: The Clinical and Pathological Findings in Interauricular Septal Defects. A Report of Four Cases. Bull. Johns Hopkins Hosp. 63: 61, 1938.

The essential pathological findings are a widely patent foramen ovale, great dilatation and hypertrophy of the right auricle and the right ventricle, and relative enlargement of the pulmonary artery and its branches and a small ventricle and aorta. This syndrome is usually associated with some condition, such as a left side valvular lesion or hypertension, which causes increased pressure in the left auricle. The characteristic enlargement of the right auricle and ventricle may occur, however, in the absence of any demonstrable increased strain on the left side of the heart.

On physical examination the significant findings are as follows: A frail individual with left-sided chest deformity, marked cardiac enlargement of the right auricle and the right ventricle, and usually a harsh systolic murmur and thrill in the second and third left interspaces; clubbing and cyanosis are absent.

The x-ray picture shows four distinctive features, i.e., great enlargement of the right side of the heart, a prominent pulmonary conus, a small aortic knob, and increased hilar shadows.

The sequelae which are of such common occurrence as to be of diagnostic aid are cardiac arrhythmias, superimposed rheumatic infections, pulmonary infections, paradoxical emboli, and the freedom from subacute bacterial endocarditis.

AUTHOR.

Lyon, James Alexander: The Interpretation of Certain Cardiac Signs in Children Bol. Soc. cubana de pediat. 10: 402, 1938.

At the Cardiac Clinic of The Children's Hospital, where a large number of children have been followed for a period of years, it has been found that the cardiorespiratory and the constant or occasional systolic apical murmur occurring in a well-nourished, nonrheumatic child are not evidence of rheumatic heart disease. A child's activities should not be restricted on the basis of these murmurs alone.

It has been observed that among those patients who have an attack of rheumatic heart disease, a small number will become clinically free of all symptoms and signs of the disease, including murmurs.

The myocardium in some cases may be extensively involved without an accompanying valvular pathology. Cardiac dilatation alone may produce murmurs that are clinically indistinguishable from those produced by mitral stenosis and incompetency and by aortic stenosis and regurgitation. In certain cases there will be a concurrent disappearance of both cardiac dilatation and valvular murmurs.

A child who has a persistent systolic apical murmur following a single attack of rheumatic heart disease should not have his activity curtailed, provided that his response to effort is normal and there is no evidence of active infection.

AUTHOR.

Leiter, Louis: Unusual Hypertensive Renal Disease. J. A. M. A. 111: 507, 1938.

Three cases are reported of organic kidney disease associated with hypertension with complete pathologic studies.

The first case is one of thromboarteritis obliterans of small renal arteries. Acute hypertension and failure of the left ventricle were present for several months without significant impairment of renal function.

In the second case chronic arteriosclerotic occlusion of the main renal arteries was associated with chronic hypertension, renal insufficiency, retinal arteriosclerosis, and contracted kidneys.

These two cases are analogous, clinically, to the Goldblatt experimental hypertension.

In the third case there were various congenital anomalies of the urinary tract leading to marked atrophy of both kidneys. The causes of the hypertension in this patient were uncertain. Certain congenital anomalies of the urinary tract are apparently regularly associated with hypertension, while other types show a much lower incidence. With both types the kidneys may be markedly contracted. The reason for the presence or absence of hypertension is unknown.

Chronic pyelonephritis is commonly productive of hypertension. The exact mechanism is not clear.

NAIDE.

Hausner, E., and Allen, E. V.: Thrombo-Angiitis Obliterans of the Brain. Proc. Staff Meet. Mayo Clin. 12: 653, 1937.

Thromboangiitis obliterans usually affects arteries of the extremities. Twenty-three instances of involvement of the blood vessels of the brain have been reported in the literature and fourteen have been encountered at the Mayo Clinic in the study of 500 cases of thromboangiitis obliterans. Of the cases reported in the literature, there were six in which the clinical history of organic changes in the peripheral vessels made them acceptable as true examples of thromboangiitis obliterans with involvement of the cerebral vessels and in which results of necropsy examination of the brain were reported. In one case embolism was said to be present; in two cases the cerebral arteries were involved by both inflammation and sclerosis; in two cases there was sclerosis only; and in two cases the inflammatory processes characteristic of thromboangiitis obliterans of the extremities were found. In the fourteen cases observed at the Clinic the diagnosis of thromboangiitis obliterans of the peripheral arteries was proved by microscopic examination, and the clinical history and findings were characteristic. Neurologic manifestations disappeared and recurred rather rapidly in several cases. Hemiplegia, which was the most outstanding manifestation, may last for several years or days and later another attack of hemiplegia may occur. Associated with the hemiplegia there may be symptoms such as confusion and irrational behavior. In three instances hemiplegia preceded the symptoms of involvement of the peripheral arteries. Disorders of behavior and psyche are not unusual. A very common complication is hemianopsia. In this study of 500 cases of thromboangiitis obliterans there was evidence of cerebral involvement in about 3 per cent. This study emphasizes that cerebral lesions in thromboangiitis obliterans occur and that peripheral thromboangiitis obliterans may be the least serious part of a disease which may disable or terminate life as a result of involvement of such vital structures of the brain and heart.

AUTHORS.

Holman, Russell L., and Self, Edward B.: The Ability of Lymph to Maintain Viability in "Devascularized" Lymph Nodes. Am. J. Path. 14: 463, 1938.

Studies were made on the ability of lymph per se to keep tissues alive. The vascular and lymphatic connections of popliteal nodes in dogs were completely severed and the nodes replaced in the popliteal space. All the nodes underwent massive necrosis.

When the authors severed all blood vascular connections but left one or more afferent and one or more efferent lymphatics intact, the nodes remained viable. The observations imply a nutritive function on the part of lymph.

NAIDE.

Veal, James Ross: Direct Visualization of the Axillary and Subclavian Veins. Radiology 31: 183, 1938.

A method of directly visualizing the axillary and subclavian veins by use of thorotrast is presented.

A number of normal and abnormal venograms are included.

The value and limitations of this method are discussed.

NAIDE.

Bowesman, Charles: Intra-Arterial Glycerin Treatment of Elephantiasis. Brit. J. Surg. 26: 86, 1938.

When glycerin is placed in contact with living tissue, it causes a movement of tissue fluid from the tissue spaces toward the vessels or region in which the glycerin is placed.

Injection of 2 to 3 c.c. of sterile 10 per cent glycerin into the femoral artery, repeated at weekly intervals, affords a simple and safe method of alleviating to some extent elephantiasis of the leg due to filaria. Intravenous injections produce an effect on the limb, though less marked.

Early cases showed marked reduction in the size of the limb. Late cases showed some improvement. The dull aching discomfort is in all cases much lessened.

Five months after treatment patients showed limbs which either had the same size as at the end of the treatment or remained smaller than before the commencement of treatment.

NAIDE.

Lueth, Harold C., and Hanks, Thrift G.: Unusual Reactions of Patients With Hypertension to Glyceryl Trinitrate. Arch. Int. Med. 62: 97, 1938.

Severe reactions not infrequently follow the administration of glyceryl trinitrate to patients with hypertension. The nature and frequency of these reactions were studied. Fifty patients with essential hypertension or hypertensive heart disease were selected from the outpatient dispensary. A chemically assayed solution of glyceryl trinitrate was carefully administered directly under the patient's tongue with an accurately graduated pipette. All tests were made under standard basal conditions, and frequent blood pressure readings were made. Nine patients (18 per cent) showed reactions, i.e., nausea, vomiting, syncope, collapse, and involuntary passage of urine and feces. These followed doses as low as 0.24 mg. (1/300 grain) and were more severe when the patient was sitting up than when he was recumbent. All the patients recovered completely within an hour. Four well-known clinical procedures were applied in these cases in the hope of determining unusual vasomotor lability. The Hines-Brown test, the histamine flare test, and changes in the pulse volume and observations of the capillaries of the skin were of no assistance in predicting these reactions.

AUTHOR.

Book Review

HEART FAILURE: By Arthur M. Fishberg, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. 788 pages, illustrated, cloth $8.50. Philadelphia, 1927, Lea and Febiger.

This book represents a summary of all the important knowledge concerning circulatory failure. It includes not only an excellent presentation of the clinical aspects of the subject but a correlation of these with the advances made during recent years in the pathology, biochemistry, and especially in the physiology of the subject. Beginning with a classification of circulatory syndromes into heart failure and peripheral failure, there is a brief mention of the subdivisions of each, followed by a series of chapters devoted to the various circulatory functions such as cardiac output, velocity of blood flow, blood volume and arterial and venous pressures. The several following chapters are concerned with such important manifestations of heart failure as edema, dyspnea, and cyanosis. The relation of heart failure to disorders of the lungs, kidneys, and nervous system is then considered. After a section in which the mechanism of heart failure is summarized, the important aspects of cardiac enlargement, gallop rhythm, cardiac murmurs, and pain arising in the heart are discussed. Several chapters follow dealing with the various conditions under which left-sided and right-sided heart failure occur. The next section, which deals with peripheral circulatory failure, is especially good in that the great importance of this syndrome in medical as well as in surgical disorders is adequately emphasized. The final sections of the book are concerned with therapy.

It is not possible in the brief space available for review to do justice to this excellent book. Every chapter reveals evidence of extraordinary scholarship. The author has an unusually broad knowledge of the subject and displays deep insight into the problems discussed. Like all good books, this one has a few weak points. Most students of heart failure will not agree with the author's statement that this disorder is always characterized by congestion as the dominant manifestation. A seizure of unconsciousness due to heart block is surely a form of heart failure, but congestion is the least important feature of the attack, the main disturbance being an inadequate blood supply to the brain. However, the author is quite correct in emphasizing that in the ordinary forms of heart failure congestion back of the failing chamber rather than inadequate output of the failing chamber is the cardinal feature. One can also take exception to certain points in the author's classification. For instance, the author classifies the heart failure produced by paroxysmal tachycardia as "hypodiastolic" failure resulting from inadequate filling as the result of the rapid rate. Actually, when failure does supervene in such cases it is associated with cardiac dilatation and hence the condition is more analogous to the ordinary "hyposystolic" failure than to the "hypodiastolic" failure due to such disorders as pericardiac effusion. However, no classification can be perfect and Fishberg's is probably as good as any that can be made and has the advantage of simplicity. The flaws in the book are of minor import and are few, while the advantages are many. The practical sections dealing with diagnosis and therapy are excellent, while the sections concerned with discussions of the theoretic aspects are perhaps even better. Fishberg's book will prove a valuable guide for the student beginning his contacts with cardiac disease, for the busy practitioner interested only in practical knowledge, and for the internist who already knows heart disease but wants to know it better. Every investigator in the field of cardiovascular disease can profit by reading this splendid book.

TINSLEY R. HARRISON.

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Original Communications

PAROXYSMAL AND PERSISTENT HYPERTENSION IN ASSOCIATION WITH LESIONS OF THE ADRENAL GLANDS

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SANTA BARBARA, CALIF.

IN THE attempt to unravel the enigma of hypertension it has become apparent that the adrenal glands, in some instances at least, are implicated. Between the opinion of Goldzieher that the adrenals are altered in practically all instances of hypertension and are fundamentally concerned with its course, and the opinion of those who hold, on the contrary, that the adrenals are little or not at all concerned, there is now established a middle ground. The relation of hyperplasia of the cortex and of tumors of both the cortex and the medulla of the adrenal gland to paroxysmal and also sustained hypertension is now definitely proved, and both Goldzieher and Bauer give specific instances in which hyperplasia of the medulla has been held responsible for hypertension. Furthermore, the experimental work of Goldblatt[1] has shown that hypertension fails to occur in dogs whose renal arteries have been compressed with metal clamps if the adrenal cortices have been previously removed, and subsides in dogs with well-established hypertension whose adrenal cortices are later removed.

In establishing the relationship of the adrenal glands to hypertension, the reporting of instances in which this relationship has been proved by post-mortem examination or by surgical intervention has, to date, been of first importance. This paper summarizes such of these clinical instances as we have been able to find in the medical literature. To these instances we have added two of our own. The first is unlike other reported cases in that marked hyperplasia of the adrenal cortex and a cortical adenoma were apparently responsible for the development of hypertension in spite of the presence of definite cardiac decompensation. The second is an instance in which the symptoms at first simulated angina pectoris, but a diagnosis of medullary adrenal

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tumor was later made, and confirmed by operation; the successful removal of the tumor resulted in permanent relief of symptoms, including the paroxysmal hypertension.

Oppenheimer and Fishberg,[2] in reporting an instance of hypertension due to cortical adrenal hyperplasia, gathered the previous cases of this kind from the literature, beginning with Edmund Neusser's observation, in 1898, of two patients who ran a clinical course of nephritis with hypertension. At necropsy, the kidneys and arteries were found to be normal. There was in each instance a neoplasm of the suprarenal gland, described as a carcinoma. Vaquez (1904) demonstrated that diffuse hyperplasia and circumscribed adenoma formation in the suprarenal cortex were frequently found in hypertensive individuals. Aubertin and Ambard (1904) reported four instances of diffuse cortical hyperplasia associated with hypertension, and three of cortical adenoma. Bland-Sutton (1918) recorded an instance of tumor of the suprarenal cortex in which there was an enormous cardiac hypertrophy for which no other cause could be found. Mackintosh (1920) recorded an instance of a 14-year-old boy with obesity, hirsuties of the forehead, eyebrows, chin, axilla, and pubis, and striae atrophicae on the abdomen. The blood pressure was 240/170. The left lower ribs bulged. The author considered this an instance of suprarenal hyperplasia. Hoag (1923) published an instance of a 4-year-old girl with precocious sexual development. The blood pressure ranged from 160/100 to 145/90. A hypernephroma was revealed at autopsy, associated with arteriosclerosis of the pial vessels.

In Table I the recorded instances of hypertension that are attributed to hyperplasia or tumor of the adrenal cortex are listed.

Our Case 1 differs from any of these in that a woman, 62 years old, whose blood pressure had been low for many years (90/60) began, in the face of very evident cardiac decompensation, to develop an increased pressure. It rose gradually over a period of one month to 180/100, and maintained this level uniformly for four months. During this period marked anasarca was continuously present. The patient died of congestive heart failure. The possible causes of this persistent increase in pressure during the course of very evident cardiac decompensation were basophilic adenoma of the pituitary gland, or hyperplasia or tumor of the adrenal gland. A roentgenogram of the sella demonstrated no enlargement. Cushing's syndrome was not evident in this patient. A slowly growing epithelioma near the right labium, which had twice been removed, suggested the possibility of a metastatic malignant growth in one of the adrenal glands.

REPORT OF CASE

CASE 1.—*History:* A woman, aged 62, was examined in February, 1934. The complaints were fatigue and anorexia for six months; a small tumor in the right side of the vulva; intermittent swelling of the ankles and face toward evening, absent

the following morning, for three months; and shortness of breath during the night requiring many pillows, for six weeks. Previous illnesses included typhoid fever at the age of 24 years and influenza at 60. Early in 1930 she noted a lump in the right labium, which grew slowly until it was the size of an egg. It caused little discomfort but occasioned some disagreeable discharge. On July 14, 1931, after a few days of fever and of swelling in the right groin, a gland was drained and part of the tumor removed. The diagnosis on this tissue was basal cell carcinoma. The wound healed promptly. No postoperative radiation was given. In January, 1932, the lump had returned. Biopsy of this tissue was reported as showing "malignant characteristics." At this time weekly subcutaneous injections of a "cancer cure serum" were given. In February, 1933, a vaginal growth was removed by electrocautery. The wound healed promptly. The "cancer cure serum" was continued. There followed periods of physical overwork and attempts to reduce the weight (212 pounds) which she had maintained for many years.

General Examination.—Height 5 feet, 6 inches; weight 206 pounds. The bony frame was large. The face was of hexagonal shape. Adipose tissue was abundant but rather uniformly distributed over the entire body. The skin had an alabaster tint; it was very dry. The outer third of the eyebrows was thin. The hair of the scalp was rather thin, fine in texture, and dry. There was little or no hair over the torso and extremities. There was moderate pitting edema of the hands, fingers and ankles. The sclerae showed a slight icteric tint.

The heart was hypertrophied; in the orthodiagram the transverse diameter was 15.3 cm., with a chest width of 24.0 cm. The width of the great vessels was 5.0 cm. The rate was 80 per minute, with normal rhythm. There was a soft systolic murmur in the second right intercostal space which was transmitted to the great vessels. The blood pressure was 100/60.

Fine moist râles were present at the base of each lung. Roentgenograms showed that there were increased bronchial markings about the right hilum. The lung fields were otherwise clear. The left side of the diaphragm was level with the right; they moved equally.

The edge of the liver was felt on deep inspiration; it was firm, smooth, and not tender.

There was an extensive scar about the vulva and high in the vagina on the right. There was a more suspicious, harder, pea-sized mass just beneath the scar, an inch inside the vagina. There was an indurated area on the right vulva which measured 1 by 0.5 cm.

Laboratory Examinations.—The urine showed a trace of albumin, with 15 to 20 leucocytes to a microscopic field. There was a hypochromic anemia; the hemoglobin was 75 per cent, the erythrocyte count 3,670,000, the color index 1, the leucocyte count 5,900, and the differential leucocyte count normal. The blood Wassermann reaction was negative. The blood sedimentation rate was within normal limits. The basal metabolic rate was minus 29 per cent. The electrocardiogram gave evidence of left ventricular preponderance.

Course.—The patient was followed for a period of six months, until the time of her death, July, 1934. Repeated blood pressure determinations during February gave no reading higher than 115 systolic, 60 diastolic. During March the pressure rose steadily until in the latter part of the month a reading of 180/100 was obtained. The pressure was maintained at this level until shortly before death. Edema became more and more marked, until general anasarca was present. Digitalization and diuretics did not lessen the edema. The heart rate varied from 70 to 104.

Blood chemical studies, which at first had shown nothing abnormal, gave the following results in July: nonprotein nitrogen 167.8 mg. per 100 c.c.; uric acid

12.2 mg. per cent; creatinine 5.7 mg. per cent; sugar 156 mg. per cent; cholesterol (whole blood) 176 mg. per cent. These values remained essentially unchanged until the end.

The nodule on the right labium grew slowly, reaching a maximum size of 3 by 1 cm. No evidence of metastases on physical examination or on repeated roentgenologic examinations was obtained.

The urine just before death contained large amounts of albumin and hyaline, granular and renal failure casts.

Autopsy.—One thousand cubic centimeters of bloodstained yellow fluid were collected from the abdominal cavity, and it was estimated that another 300 c.c. escaped measurement. The free edge of the liver was the width of three fingers below the costal margin. There were collected from the pleural cavities 1,350 c.c. of blood stained fluid. The pericardial fluid amounted to 50 c.c. and was slightly cloudy.

The heart weighed 520 gm. The pericardial surface was dull and was covered with a thin layer of fibrin. The maximum thickness of the wall of the left ventricle was 2 cm., and that of the right, 1 cm. The coronary orifices were patent, the walls thin. The lining of the aorta was smooth throughout. The remainder of the gross observations are not pertinent to this report.

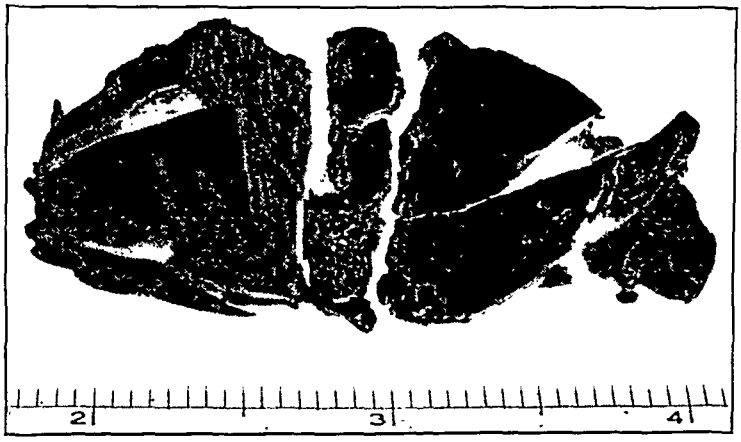

Fig. 1.—Tumor right adrenal cortex, at autopsy. Case 1.

The right adrenal gland weighed 27 gm. and measured 6 by 3.5 by 2.5 cm. Surfaces made by cutting were soft in consistency and yellow in color. The left adrenal weighed 10 gm. and measured 5 by 3 by 0.6 cm.

The left kidney weighed 141 gm. Its capsule stripped with ease. The surface was slightly granular. On surfaces made by cutting, the cortex was 5 mm. in thickness and pale. In several regions it was sharply demarcated from the medullary pyramids, which were beefy red. The lining of the pelvis was smooth, gray, and glistening. The right kidney weighed 125 gm. Surfaces made by cutting were similar to the left kidney.

The liver weighed 2,090 gm. Its surface was smooth and firm. Surfaces made by cutting were about 20 per cent yellow with fat and had a nutmeg appearance. The spleen weighed 360 gm. The parenchyma was firm and slate-purple in color.

The pancreas and the thyroid were normal and weighed, respectively, 150 and 19 gm.

The uterus and ovaries were small, but of normal proportion. There was a slightly raised red-brown nodule in the middle of the right labium majus, 2 cm. in diameter and elevated about 5 mm.

Permission for examination of the brain was refused.

Anatomic Diagnoses.—Marked generalized hypertrophy and dilatation of the heart; fibrinous pericarditis; marked anasarca; hypostatic hyperemia and edema of the lungs; passive hyperemia of the liver; cyanotic induration of the spleen; adrenal cortical hyperplasia; cortical adenoma; tumor nodule of the right labium majus; obesity.

Histologic Examination.—There was a uniform and diffuse hyperplasia of the entire cortex of the left adrenal, its average width being 3.5 mm. On sectioning the entire gland, adenomas were not found. There was a marked hyperplasia of the entire cortex of the right adrenal. In addition, there was a large nodule in the cortex, poorly demarcated. It measured 4 by 2 cm. On gross section it appeared histologically of the same structure as the cortex itself. The cells of the cortex of the right gland were arranged in a compact alveolar fashion. The nuclei appeared somewhat smaller than those of the opposite adrenal and the cytoplasm was somewhat more vacuolated. There was no evidence of any medullary elements.

In the kidneys there was moderate thickening of the walls of the medium-sized blood vessels. The capsules of Bowman were not thickened. There were no other unusual findings in the kidneys. The changes in the liver and spleen were consistent with chronic passive congestion. In the heart muscle the fibers were moderately widened. There was no scarring. In the pancreas and in the thyroid there was nothing abnormal.

In sections of the ovary there were numerous scars. The blood vessels were thickened, many of them to a point of occlusion. A few small follicular cysts were seen. There was no sign of malignancy.

COMMENT

Our report differs from any of those in the literature in that a woman, 62 years old, whose blood pressure had been low for some years (90/60 to 110/60), began in the face of very evident cardiac decompensation to develop an increased pressure. It rose gradually over a period of a month to 180/100 and maintained this level uniformly for 4 months, i.e., until a few days before her death from congestive failure. During this period anasarca was continuously present.

The possible causes of this persistent increase in pressure during the course of evident decompensation were: (1) basophilic adenoma of the pituitary gland, (2) tumor of the adrenal gland, or (3) hyperplasia of the adrenal cortex or medulla. A roentgenogram of the sella turcica demonstrated no enlargement. Cushing's syndrome was not evident in this patient. A slowly growing epithelioma in the right labium, which had been twice removed, suggested the possibility of a malignant metastatic growth in one of the adrenals. The absence of metastases in connection with this malignant lesion was attested by the autopsy examination.

Our second presentation is an instance of pheochromocytoma. The diagnosis was made before operation, and there has been complete disappearance of the symptoms since the tumor was removed a year ago.

To date, there have been approximately eighty-five instances of pheochromocytoma reported in the literature. In only twenty was a

clinical diagnosis made. Undoubtedly, a considerable number of these tumors are masquerading under a variety of symptoms and so escaping detection. Clinicians of the future, however, will be enabled to make more clear-cut diagnoses through roentgenologic studies preceded by the injection of air about the adrenal glands, after the method first described by Carelli and modified by Cahill, Loeb, et al.,[3] of New York City. In many instances, this will also eliminate the necessity of an exploratory incision on one side in the hope that the suspected tumor will lie on that side, and will determine whether or not there is an adequately functioning adrenal on the opposite side. Autopsies have shown that in 15 to 20 per cent of the cases the adrenal on the side opposite the tumor had functioned inadequately.

REPORT OF CASE

CASE 2.—*History:* This patient, a man, 56 years old, was first seen by us on July 27, 1936. His chief complaint was that he had been suffering from increasingly frequent "attacks" which were initiated by a feeling of dizziness, followed by nervousness and apprehension, a generalized headache, and palpitation of the heart. More recently there had been a pressure pain over the precordium which at times became intense and was then accompanied by marked shortness of breath. This pain did not radiate down the arm or up to the neck. The attacks usually occurred soon after he arose in the morning and before he had eaten anything. He stated that his wife could always predict the oncoming weak spell by his pallor, and that flushing of the skin became apparent as the symptoms subsided. During the subsidence he was conscious of tremor, weakness, fatigability. Usually the whole disturbance would last a relatively short time, from thirty seconds to fifteen minutes.

He was free of symptoms referable to the cardiorespiratory, gastrointestinal, or genitourinary system. His past history was negative, except for a severe streptococcus sore throat at the age of 45 years and erysipelas at the age of 50. His father died at the age of 81 of carcinoma of the stomach; his mother at the age of 42 years in childbirth. Three brothers died in childhood, and one sister at the age of 60 of some illness involving the nervous system. One sister was said to have had episodes similar to those of this patient, but had had no recurrence for some months.

General Examination.—Blood pressure 140/95; pulse rate 80; temperature normal. The chest was barrel-shaped, the expansion slightly limited. No evidence of fluid or congestion was found. The heart was not enlarged; the rhythm was normal, the sounds of good quality. An inconstant, blowing, untransmitted systolic murmur was heard at the apex. All of the peripheral arteries, including the dorsalis pedis, pulsated. The vessel walls seemed slightly thickened. The abdomen, genitalia, rectum, and extremities were negative.

Laboratory Examinations.—Kidney function tests showed slight impairment of the urea clearance (I C_s- 47.0 per cent; 25.4 c.c. II C_s- 46.3 per cent; 25.0 c.c.); normal excretion of phenolsulphonephthalein by ureteral catheterization; good concentration in the Volhard test on two occasions (specific gravity 1.006 to 1.030, and night volume 225 c.c.). A slight trace of albumin was noted on one occasion, but otherwise urinalyses were negative. The blood counts were normal. The icteric index was under nine. The blood Wassermann reaction was negative. The complexes of the electrocardiogram were essentially normal; there were occasional ventricular

extrasystoles. After an Ewald test meal the free hydrochloric acid was zero, the total acidity 11°. Basal metabolism determinations were not successful because of the early morning attacks suffered by the patient.

After the first examination the number of seizures for a time became much less and were mild in degree. When, for no reason that could be determined, the attacks again became more frequent and severe, the patient was hospitalized, March 18, 1937, and carefully studied for suspected adrenal disturbance. Attacks were at first initiated by carotid sinus pressure and the phenomena studied at will. Later, exercise before breakfast was sufficient stimulus to bring on an attack (Fig. 2). A relative bradycardia was noted in relation to the height of the blood pressure. During the attacks the heart sounds were loud. Many extrasystoles were present.

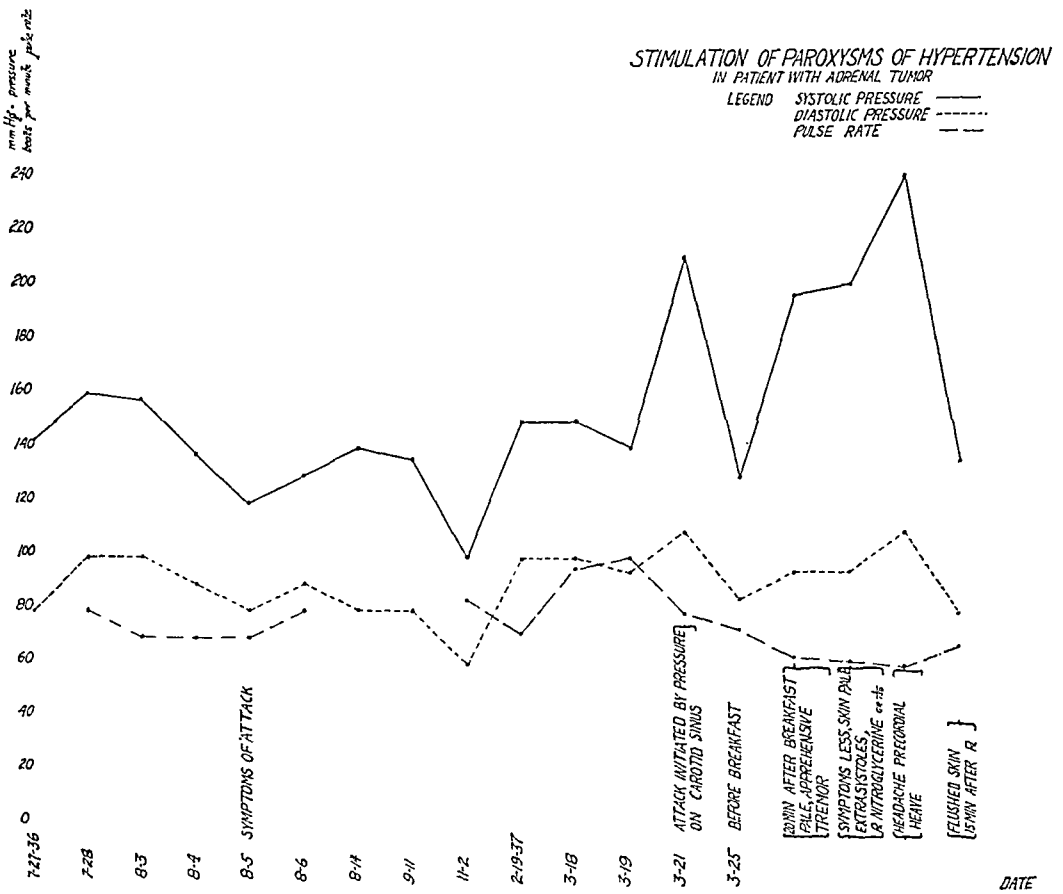

Fig. 2.—Episodes of hypertension induced by carotid sinus pressure and by exercise before breakfast.

The episodes of paroxysmal hypertension are illustrated in Fig. 3. These episodes occurred frequently, and it is probable that changes in the pressure were more abrupt than the records show. The attacks seemed to occur spontaneously. When the patient complained of dizziness, he would be quite pale and his extremities were cold and damp. He had an apprehensive expression, and complained of substernal pain and a feeling of shortness of breath and nausea. These symptoms would come and go as long as he remained pale. Later his face would flush and the symptoms would subside; this was followed by perspiration and a trembling of the hands and body.

Because of the vasomotor instability shown in the attacks and the variations in blood pressure, hyperadrenalinism was suspected. A glucose tolerance test revealed

mild intolerance (144, 166, 118, 88 mg. per 100 c.c. whole blood), which supported this belief. Gonadotropic hormone was not present in the urine. This test, as suggested by Frank,[4] should be made in all instances of suspected tumor of the adrenal glands. If an adrenal gland tumor is composed of cells of the adrenal cortex, the gonadotropic hormone will likely be present in the urine. Since it was absent in this instance, we felt that the tumor must be a pheochromocytoma, or less likely, that there was medullary hyperplasia. Goldzieher[5] cites four cases which he believes show significant relation between adrenal hyperfunction and hypertension. In each case one or more nodules were present, together with diffuse hyperplasia of the medulla. In two of the cases there was clinical evidence of hypertension. He be-

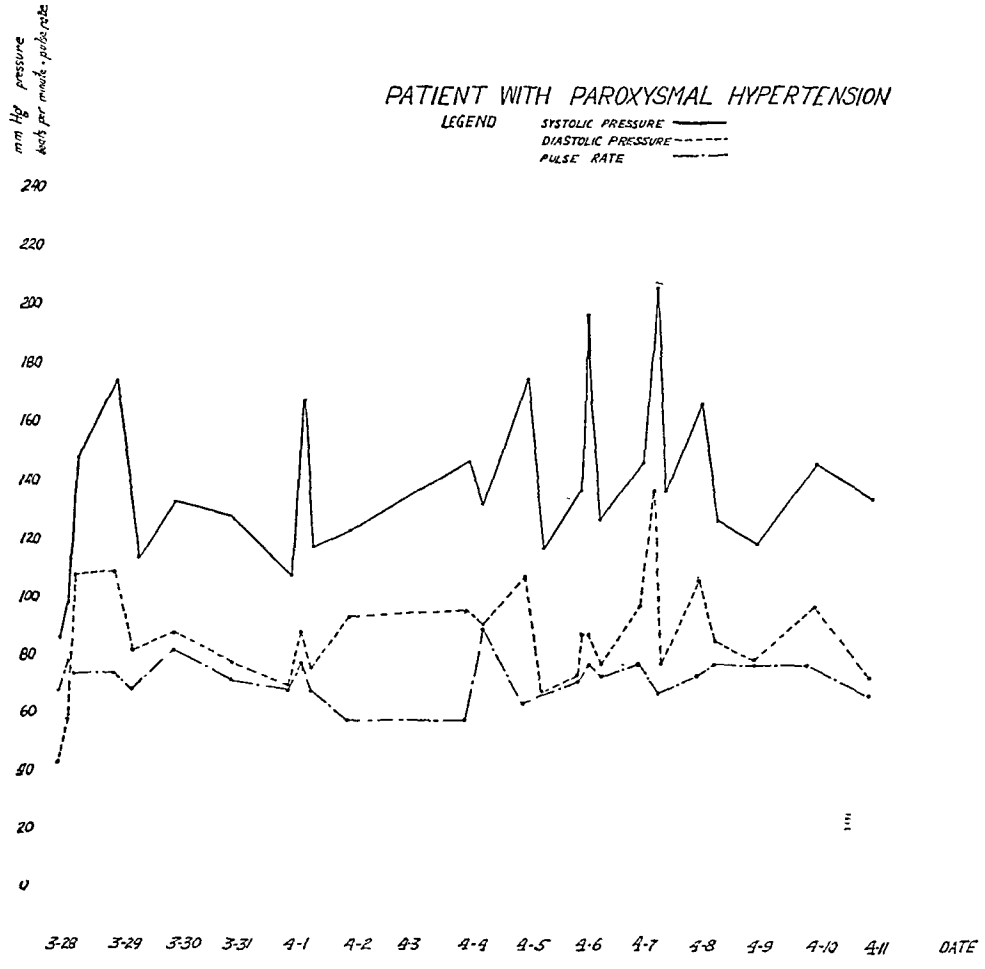

Fig. 3.—Episodes of paroxysmal hypertension induced by exercise.

lieves that the clinical manifestations of nodular hyperplasia do not differ essentially from those observed in cases of pheochrome tumors. Quantitative differences may exist and explain the rapid progress, paroxysmal character, and early fatal outcome in tumor cases, in contradistinction to the insidious onset, slow progress, and protracted course of hypertensive disease in the presence of nodular hyperplasia.

To further verify the diagnosis, perirenal air injection studies were made, after the method of Carelli as modified by Cahill et al.,[3] in conjunction with retrograde pyelography, and these studies revealed enlargement of the right adrenal shadow (Fig. 4).

With the diagnosis of a tumor of the right adrenal area thus established, an operation was performed by Dr. Samuel Robinson on April 12, 1937. When the adrenal gland was first manipulated during the course of the operative procedure, a paroxysm

Fig. 4.—Perirenal air injections.

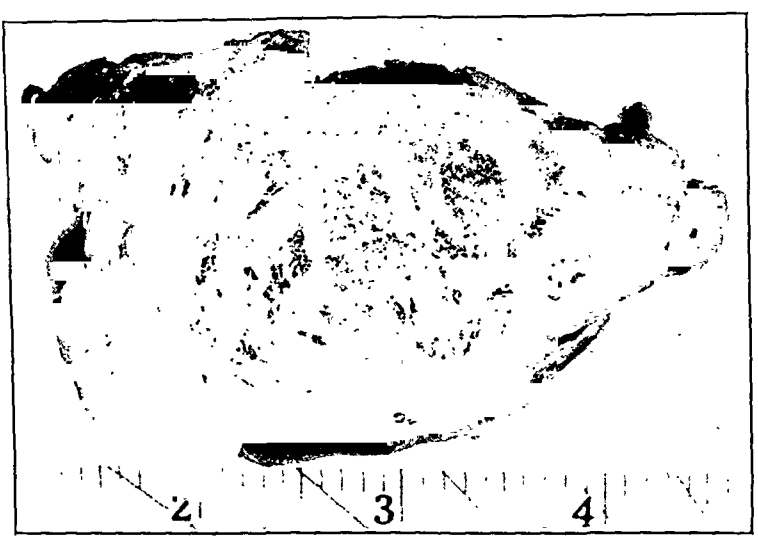

Fig. 5.—Right adrenal gland removed at operation. Case 2.

of hypertension was induced, the blood pressure rising suddenly from its usual level of 140/80 to 240/140. The paroxysm lasted approximately five minutes. Shortly after the adrenal gland and the tumor were removed the pressure dropped to a very low level (64/30). At this point in this operative procedure and for many hours thereafter hypoadrenalinism may exist, in which case proper therapeutic procedures should be instituted. Other readings made during that day were 98/50,

100/70, 96/80 (Fig. 6). The following day pressure readings higher than 112/74 were not obtained, but on the second day the pressure had returned to the preoperative level of 140/80.

The postoperative course was uneventful, and the patient was discharged from the hospital May 6, 1937. During the year that has elapsed since the operation there have been no recurrences of his former attacks, and the blood pressure has ranged from 120/80 to 140/80.

Pathologic Report.—The adrenal gland measured 3.5 by 2.3 by 2.2 cm. The midcavity was expanded by a gray-yellow, moderately firm mass of tissue which was bounded everywhere by a thin layer of yellow cortex 1 to 2 mm. thick. The cortex

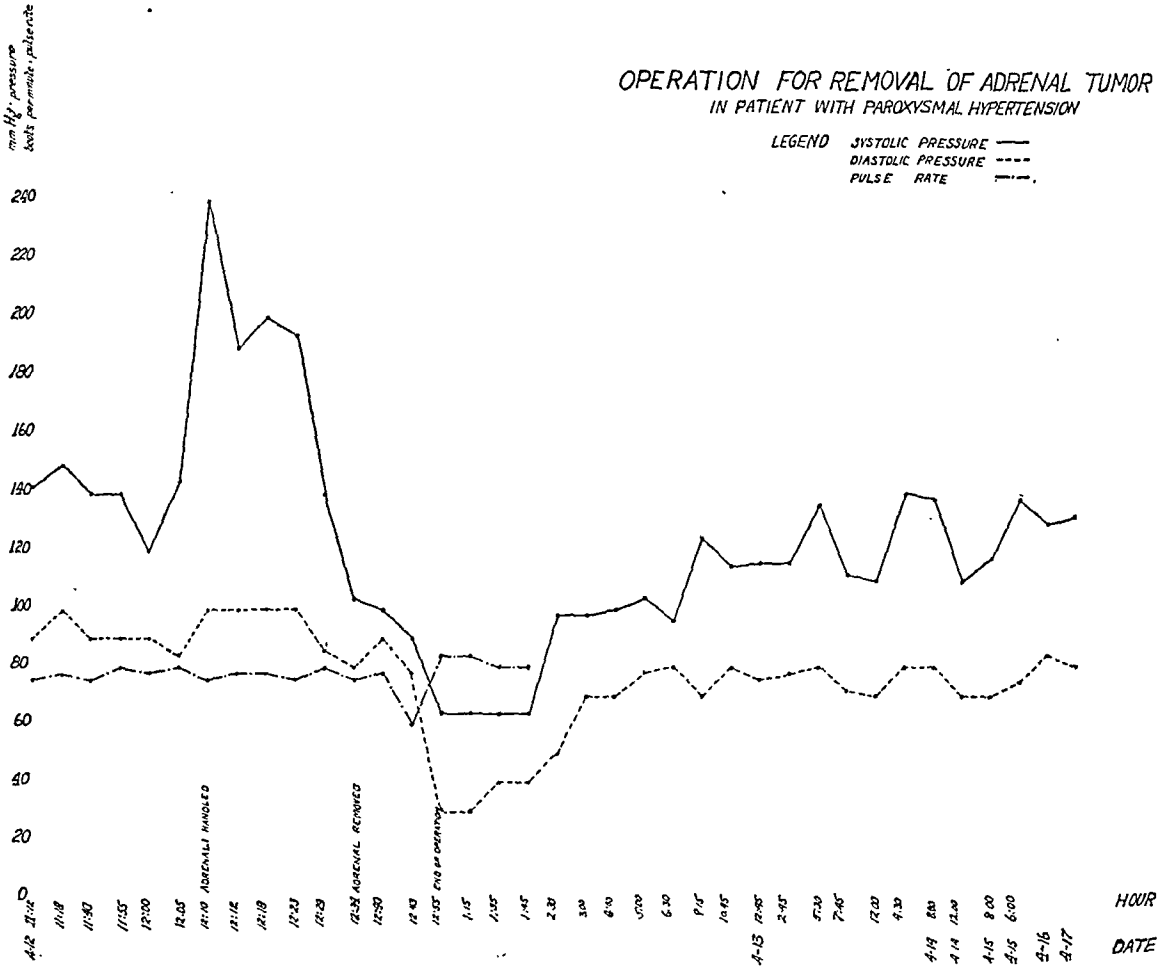

Fig. 6.—Blood pressure changes induced by handling adrenal gland at operation, showing fall of pressure following removal of gland and gradual return to normal over a period of two days.

of the gland was only 1 mm. thick. There was next a thin layer of rather acellular fibrous tissue. The tissue below this was composed of round or oval cells, some of which contained mitotic figures. Their cytoplasm was vacuolated; the cells remained in solid sheets. The pathologic diagnosis was pheochromocytoma of the right adrenal gland.

Extracts of the tissue were made by the trichloracetic method. The yield of adrenalin was equal to that of a normal gland. The specimen was frozen after removal in an effort to preserve the adrenalin from oxidation. This process may have delayed, but not completely stopped, the reaction of oxidation, and thus a portion of the yield may have been lost. Prior to the operation, two attacks were in-

duced with the intention of emptying the tumor of adrenalin and thus preventing a seizure during operation. However, a third attack did occur while the gland was being mobilized.

COMMENT

This patient's substernal compression and fear of impending dissolution at first suggested angina pectoris. He was conscious of fast heart rate and breathlessness, and was told that his face had marked pallor, followed by flushing. Sometimes there were nausea and vomiting. Later, extreme fatigability, tremor, and indisposition were noted. There were the characteristic paroxysms of hypertension, which have completely disappeared, with the other symptoms, since removal of the pheochromocytoma.

The differential diagnosis is usually limited to the group of hypertensive states, although pheochromocytomata may be present without a resulting hypertension. Essential hypertension is simulated, but the stimulation of the sympathetic nervous system is much more striking in those patients who have pheochromocytomata. The peripheral vessel change is dramatic in this group. The reactions are out of proportion to the physical findings between attacks. Similar symptoms and findings may be noticed in hyperplasia of the thyroid, as in toxic goiter, in which instance, however, the stimulation of the autonomic system is not as marked. The hypertension of toxic goiter is merely a rise in systolic pressure and is more usually sustained after it is once acquired. Again, the paroxysmal seizures are more clearly defined in medullary tumor. Cushing's syndrome simulates very closely adrenal cortical tumor and should be borne in mind in each instance in which disease of the adrenal gland is suspected. The important diagnostic points in pheochromocytoma are paroxysmal hypertension, increasing intolerance to glucose, and roentgenologic evidence of enlargement of an adrenal gland.

The reason for the paroxysmal type of hypertension is a matter of conjecture. Some writers feel that a psychic disturbance will cause an excretion of adrenalin because of the intimate manner in which these tumors are connected with the autonomic nervous system. Others feel that, because of the position of the gland, change in posture produces pressure and thereby stimulates excretion of adrenalin.

Briefly, the symptoms and signs of this condition are: a feeling that the heart is beating fast, breathlessness, pallor of the face followed by flushing, and sometimes nausea and vomiting. Later, extreme fatigability, tremor, and indisposition will be noted. There are usually a paroxysm of hypertension and an increase in pulse pressure, but a relatively slight increase in heart rate. The skin will be blanched and later flushed. There may or may not be glycosuria. There is a decrease in sugar tolerance. Signs of congestive heart failure may be present.

Excellent reviews of the earlier cases have been given by Rabin,[6] Eisenberg and Wallerstein,[7] and Belt and Powell.[8] The first mention of such a tumor was made by Frankel, in 1886. Manasse, in 1893, described the histopathology in detail, and later (1896) discovered the affinity of the tumor for the salts of chromic acid. Robert, in 1899, was the first to mention that hypertension existed in a patient with one of these tumors, although apparently he did not suspect the direct connection. In the thirty-seven cases reported prior to 1922 there was no definite suggestion of symptoms connected with these tumors. It is true that several operations were terminated suddenly with shock and death, and at intervals patients were known to have suffered hypertension. The first clinical description of paroxysmal hypertension was given in 1922 by Labbe, Tinel, and Doumer.[9] Their patient, a woman 28 years of age, suffered malaise, pallor, and the flushing of vasomotor instability, and died as the result of pulmonary edema. Paraganglioma was found at necropsy.

The first report of operative removal of such a tumor, with relief of symptoms, was made by C. H. Mayo (1927).[10] Further successful operations were reported by von der Muhll (1928),[11] Shipley (1929),[12] and Porter and Porter (1930).[13]

In 1934, Belt and Powell[8] attempted to remove a pheochromocytoma *in a patient with paroxysmal hypertension. The shock was too great* and the operation was terminated prematurely, the patient dying shortly afterward. Their failure to make a correct clinical diagnosis in this patient who, they felt afterward, presented such an extraordinarily dramatic group of signs and symptoms, was the stimulus for their excellent study of the clinical syndrome associated with the pheochromocytomata of the suprarenal medulla.

In this same year (1934), successful operations were reported by Coller, Field and Durant,[14] and by Suermondt.[15] Labbe and Nepveux[16] described a case of paroxysmal hypertension in which the patient was cured by removal of a paraganglionoma which had arisen from chromaffin tissue outside of the adrenal gland. The follow-up period was not given, but a statement was made that the blood pressure had become stabilized at 140/100. Kalk[17] described a typical case with paroxysmal hypertension and successful operation. Bauer and Leriche[18] recorded paraganglioma of the splanchnic nerve. Donzelot's case[19] was typical, and complete recovery on removal of the tumor occurred. Ernould and Picard[20] showed that paroxysmal hypertension was present in a patient with a malignant tumor, the presence of which was betrayed by metastases to the skull and various parts of the body. Laubry and Bernal[21] followed a patient with paroxysmal hypertension which later became fixed; the patient finally died in uremia.

In 1935, McKenna and Hines[22] removed a malignant paraganglioma from a patient with a variable hypertension and reported that the patient had been symptom-free for four months thereafter. Kelly,

et al.[23] (1936), Landau, et al.[24] (1936), and Beer, King, and Prinzmetal[25] (1937), have reported successful operations for removal of tumors in patients with typical symptoms. Information in the latter article is of value in that adrenalin is proved to be the pressor substance by clinical and laboratory tests upon the blood of the patient.

Kremer[26] (1936) reported a typical case with paroxysmal hypertension, in which death was due to pulmonary edema. Fein and Carman[27] (1937) reported medullary carcinoma, with large quantities of adrenalin per unit volume. The blood pressure was consistently low. Wells and Boman[28] (1937) reported a case in which the typical clinical syndrome was not recognized by five physicians, the patient subsequently dying of operative shock following removal of an acutely inflamed appendix.

In an analysis of the cases reported, there is little variation as to sex; of the 68 in which the sex was recorded 35 were women and 33 were men. As to age, the predominance lies in the middle decades, about equally in the third, fourth, and fifth, although a tumor has been found in a child 2½ years of age and in a man of 82 years. There are, however, eight cases in which the age was not mentioned. Of the symptoms, the most frequent are those of vasomotor instability, namely, palpitation, headache, nausea, and vomiting. Dyspnea, weakness, dizziness, fatigability, pain over the precordium, diaphoresis, sialorrhea, insomnia, convulsions, and sense of hair pulling are mentioned likewise.

In thirty-six instances the blood pressure was not recorded. Of the remainder, the paroxysmal type was noted in twenty-two, the constant type in nineteen, and in three the pressure was said to be normal. In retrospect, however, studies of these histories with regard to the incidence of hypertension are not reliable. In those reports in which no pressure is recorded, it is only assumption that the pressures were normal.

The tumors vary in size and weight up to 10.5 cm. and 1,000 gm., respectively. They are found about twice as often on the right as on the left side. In six instances they were found bilaterally. In seven instances they were said to be malignant because of evidence of metastasis.

In association with pheochromocytoma, von Recklinghausen's disease was present in five, tuberculosis in five, Addison's disease and melanoderma in one each, and diabetes in five. Of course, the diagnosis of diabetes may be rightfully doubted, as the evidence is based on glycosuria alone. Some of these patients may have had hyperglycemia because of hyperadrenalinemia and a low kidney threshold, and, therefore, definite proof of pancreatic disease is lacking.

Of the forty-one cases in which hypertension was found, there were but three with evidence of kidney change and but two with atherosclerosis.

TABLE I

RECORDED INSTANCES OF HYPERTENSION ATTRIBUTED TO HYPERPLASIA OR TUMOR OF THE ADRENAL CORTEX

YEAR	CASE	SEX	AGE	BLOOD PRESSURE	PATHOLOGIC FINDINGS		REMARKS
					OPERATION	AUTOPSY	
1921	Achard, Thiers[29]	F	71	220/100	None. Died 16th day after admission to hospital.	Adrenals large, right, 9 gm.; left, 7 gm. Hyperplasia cortex. Pituitary and thyroid normal.	Heavy moustache and beard only stigmas of virilism; menstruation 12 to 60 years. Glycosuria discovered at age of 69 by accident; no diabetic symptoms. "Diabetes of bearded women." Died 16th day.
1924	Walters and Keyser[30]	F	37	124/90 to 180/110	Tumor attached to left kidney removed.	Carcinoma suprarenal. Hypoplasia right suprarenal gland.	Genitosuprarenal syndrome, striking changes in sex characteristics. Enlargement thyroid, nervousness, tremor, tachycardia, heat intolerance. Pituitary, pineal bodies, and ovaries normal at autopsy. Died 4th day following operation.
1924	Oppenheimer and Fishberg[31]	M	24	200/150	None. Diagnosis of essential hypertension made. Tumor found only at autopsy.	Right, large tumor cortex and medulla. Left, 10 small cortical adenomas (10 gm. total weight)	Had acromegalic appearance. Renal function intact. Died of bronchopneumonia a few weeks after first seen.
	Ibid.	F	12	190/130	None.	----------	Genitosuprarenal syndrome. Blood sugar 260 mg. %. Abscesses on back and neck, ulcers on legs. Patient could not be followed, but it was reported that she died 3 weeks after leaving hospital.
1927	Murray and Simpson[32]	F	36	200/120	Suprarenal tumor removed.	----------	Amenorrhea 9 months before operation; insatiable appetite, with gain in weight. Following operation, menstrual function restored; appetite and weight returned to normal. Systolic blood pressure as a rule only about 120, but easily raised to 190 or 200 on slight excitement.

TABLE I—CONT'D

1929	Faber[33]	F	48	240/110	None.	Cortical adenomas; chronic nephritis, etc., marked congestion anterior lobe pituitary.	Author remarks that findings in this case, with the exception of suprarenal changes, are those of long-standing hypertension. Believes it impossible to say whether kidney and blood vessel disease or disease of suprarenals was causative factor.
1931	Hunter, McMillan, Boyd, and Cameron[34]	F	30	185/122	Tumor detached from vaginal wall by finger.	----------	Virilism; suppression of menstruation; diabetes mellitus. Mass felt in right upper abdomen, evidently connected with right kidney; no attempt made to remove this tumor. Roentgenogram showed metastatic lesions of chest and decalcification of vertebrae. No follow-up nor report of death on this patient.
1931	Meyer and Frumess[35]	F	13	158/85	None.	Primary carcinoma left suprarenal gland, with metastases. Large cortical adenoma, right.	Precocious development; hirsuties; suppression of menstruation, etc. No evidence of nephritis. Died 7 days after admission to hospital.
1932	Plazy and Germain[36]	M	40	200/80	None.	Cortical suprarenal tumor; aneurysm aorta; very numerous atheromatous patches on walls of aorta.	Authors believed that hypertension was due to the suprarenal tumor and that the tumor also explained the accompanying atheroma.
1933	Cecil[37]	F	31	170	720 gm. tumor removed.	Adenocarcinoma of left suprarenal.	Genitosuprarenal syndrome. Patient died 12 hours after operation of pulmonary hemorrhage.
1933	Shallow[38]	F	27	140 to 220	Suprarenal tumor removed. Histologic examination: adenoma, adrenal cortex.		Manifestations closely resembled Achard-Thiers syndrome. No improvement following operation. Died 5 months later of metastases.

TABLE I—CONT'D

YEAR	CASE	SEX	AGE	BLOOD PRESSURE	PATHOLOGIC FINDINGS		REMARKS
					OPERATION	AUTOPSY	
1933	Van der Bogert[39]	F	2	160/110 (Eyegrounds showed evid. hypertens.	Right adrenal shelled out subcortically.	None, except examination of tumor mass. Diagnosis: adrenal carcinoma.	Adrenal precocity. Sella extremely small roentgenologically. No autopsy, so lesions of pituitary and pineal could not be ruled out. Died within 36 hours after operation.
1933	Player and Lisser[40]	M	5	114/70 134/80	Left adrenal cortical tumor, possibly malignant.	----------	Sexual precocity. Nineteen months after removal of tumor blood pressure had dropped to 92/40. Some modifications of endocrine abnormalities.
1933	Quinby[41]	M	12	152/90 to 170	Large retroperitoneal tumor; not removed.	Micro. exam. report, evidently from biopsy: adrenal *carcinoma*.	Died following operation. Author believes that an adrenal cortical tumor of adenomatous character had been present many years, finally becoming malignant. Patient showed precocious puberty.
1934	Craig and Cran[42]	F	28	180/118	None.	Basophilic adenoma anterior lobe pituitary. Suprarenals deeply congested. Hyperplasia cortex.	Clinically diagnosed as basophilic adenoma. Author believes adrenal and thyroid changes were secondary. Roentgenotherapy; died of pneumococcic pneumonia.
1934	Leyton[43]	M	32	170	None	Tumor thymus gland, oat cell. Hyperplasia adrenal especially cortex. No excess basophilic cells, pituitary, in serial sections.	Multiglandular disease. Face and abdomen obese and legs slender. Broad purple lineae atrophicae from pubis over abdomen, etc. Sella appeared normal.

TABLE I—CONT'D

1934	Walters, Wilder, and Kepler[44]	F	25	180/120	Adenocarcinoma.	----------	Blood pressure returned to normal after operation. Right suprarenal gland found replaced by adenocarcinoma containing tissue of suprarenal origin. Patient had gained weight; menses had ceased, etc.
———	Ibid. No. 2	F	9	132/97	Cortical adenoma, left adrenal.	----------	Genitosuprarenal syndrome began at age of 4 years. Within 3 weeks following operation weight had fallen; excessive hair disappearing. Blood pressure 98/62, 2 months later.
———	Ibid. No. 3	F	39	170/102	Tumor, left suprarenal. Adenocarcinoma.	----------	Blood pressure 130/76, 2 months following operation. Face had regained normal contours, etc. Had had increase in weight, falling hair, scalp, increased hair on body.
———	Ibid. No. 6	F	45	176/80	None.	Both suprarenals hyperplastic, combined weight 49 gm. Pituitary normal. Thymic tumor present.	Face heavy, dusky red; at times tetany present; died 2 months after admission to hospital. Thyroid previously operated upon. Multiple adenomas at autopsy in colloid thyroid.
———	Ibid. No. 7	F	32	168/118	Exploratory; adrenal glands definitely enlarged.	Combined weight suprarenals estimated twice normal. Pituitary normal.	Hirsuties, irregular menstruation, etc. Died after 10th day, pneumonia. Portion adrenals removed at exploratory operation appeared normal histologically.
———	Ibid. No. 8	F	30	150/100	Enlargement of both adrenals, hyperplasia tissue.	----------	Cortical adrenal syndrome disappeared after operation for most part. Blood pressure 124/62.

TABLE I—CONT'D

YEAR	CASE	SEX	AGE	BLOOD PRESSURE	PATHOLOGIC FINDINGS		REMARKS
					OPERATION	AUTOPSY	
1935	Lescher[45]	F	35	205/155	Suprarenal tumor, left removed.	Cortical cell carcinoma	Symptoms and signs of Cushing's disease. Died 12 hours after operation. Examination pituitary at autopsy did show general increase in basophiles and acidophile cells. Broster and Vines stain positive.
1935	Goldzieher and Koster[46]	F	27	180/100 after operation (not given before)	Left adrenal removed; both larger than normal.	----------	Had gained weight to 335 lbs.; missed periods; hirsutism present. After operation weight reduced to 190; periods regular. Blood pressure 180/100.
1935	Volini and O'Brien[47]	M	23	205/104	Tumor removed.	Malignant adenoma of suprarenal cortex.	Died in shock. Suprareno-cortical syndrome had been exhibited.
1935	Hare, Ross, and Crooke[48]	F	--	205/140	Suprarenal tumor removed.	Malignant suprarenal tumor. No pituitary tumor.	Had all signs of Cushing's syndrome, but in serial sections of pituitary no basophilic tumor found. Patient died in shock.
1935	Calder and Porro[49]	F	34	160/100 to 190/130	None. Roentgenotherapy; no benefit.	Primary adrenal neoplasm cortex.	Thought clinically to be instance of pituitary basophilism, but at autopsy pituitary was normal. Died 15 months after observation in hospital.
1935	Lyall[50]	F	30	210/120	Decompression operation. (Died following day.)	Carcinoma suprarenal.	Diagnosed as case of cerebral tumor. Eyesight failing, tingling, etc. Also obese, hirsutism, etc. Died day following operation.
1936	White[51]	F	37	155/100 variable	Exploratory only.	Adrenal cortical carcinoma (biopsy).	Patient showed all features commonly associated with adrenal cortical tumor. Subsequent course rapidly downward.

SUMMARY

This paper summarizes, first, the clinical instances that we have been able to find in the literature of hypertension ascribed to hyperplasia or tumor of the cortex of the adrenal gland. To this group we have added one case of our own which is unlike other reported instances in that marked hyperplasia of the adrenal cortex and a cortical adenoma were apparently responsible for the development of hypertension in a patient with evident cardiac decompensation.

The second presentation records the story of a patient in whom a diagnosis of pheochromocytoma of the adrenal medulla was made, with complete disappearance of the symptoms following surgical removal of the tumor.

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STUDIES ON CORONARY CIRCULATION

VI. The Effect of Some Members of the Digitalis Group on the Coronary Circulation*

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DRUGS which have generally beneficial effects on cardiac function may, at the same time, cause an undesirable alteration in the coronary circulation. It is, therefore, important to determine whether such a change occurs, and whether this change is of sufficient magnitude to be detrimental to efficient cardiac function. If it is definitely established that a drug has a constrictor action, it might be wise to consider the desirability of supplementing its action by the use of a known coronary dilator.

Since the members of the digitalis group are widely used in cardiac therapy, an exact knowledge of the pharmacologic action of these drugs is necessary in order to obtain the most satisfactory results from their use. We are particularly interested in the effect of this group of drugs on the coronary circulation. In the extensive literature and the large amount of experimental data on this problem contradictory opinions still exist regarding the effect of the digitalis bodies on the coronary circulation.

In the past it has been suggested that any undesirable coronary constrictor action of digitalis which might occur is, to a certain extent, counterbalanced by an improvement in myocardial contraction and the resultant increase in blood pressure. However, it is possible that the increased myocardial contraction actually interferes with the coronary flow, as Anrep[1] has demonstrated, and thus produces a further functional reduction in flow in a heart already embarrassed by disease or malnutrition.

The action of strophanthin and digitoxin upon the coronary circulation was studied by Loeb,[2] who perfused the excised heart of the cat with solutions of the drugs. According to his findings, strophanthin caused no appreciable change and digitoxin caused some reduction in the coronary flow. Later, Bond[3] reported that strophanthin and digitalis had no effect on the velocity of coronary flow in the intact cat. Voegtlin and Macht[4] investigated the direct action of an extensive series of drugs of the digitalis group on chains of coronary arterial

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rings. One of two digitalin preparations, digitalein, one of two strophanthin preparations, and a tincture of digitalis caused various degrees of contraction. They described digitoxin as the "most powerful coronary vasoconstricting constituent of digitalis leaf." Digitonin, digalen, and a digitalis infusion caused relaxation.

Gunn[5] reported that perfusion of the rabbit's heart at 28 to 41° C. with dilute solutions of crystalline strophanthin in nonglucose Ringer's solution caused "little or no constriction of coronary vessels."

With the description of the tampon cannula by Morawitz (1912), study of the minute volume of coronary blood flow was facilitated. Since its introduction several investigators have used this instrument in attempts to determine the effect of the digitalis bodies on the coronary circulation.

Sakai and Saneyoshi,[6] investigating the action of strophanthin on the intact cat preparation, concluded that this drug in small doses (0.01 mg.) has no direct action on the coronary vessels. According to these investigators, the increased volume of blood collected from the coronary sinus is entirely dependent on the changes in blood pressure. Larger, apparently toxic, doses of 0.2 to 0.5 mg., caused, almost always, an early fall in coronary outflow associated with a rise in blood pressure (constriction); later, in some instances, this trend was reversed and the flow increased.

Gilbert and Fenn[7] made an extensive study of the effect of digitalis on the coronary flow of intact dogs and concluded that digitalis bodies may have a vasoconstrictor action on the coronary arteries. They state that certain whole leaf preparations purchased on the open market produced constriction in the majority of their animals; one whole leaf preparation, however, had no constrictor effect. Ouabain had less constrictor action than did the whole leaf preparations. The two digitoxin preparations which they investigated caused variable responses, although there was some evidence of a coronary constrictor action. Bodo[8] investigated the changes in heart tone and coronary outflow in heart-lung preparations of dogs after administration of a number of drugs. He concluded that digitalis and strophanthin produce a moderate increase in the coronary flow.

Anrep[1] has stated that the Starling heart-lung preparation combined with the Morawitz method of collecting the coronary blood, using the same technique of measuring the blood flow in the intact animal, is the proper and the valuable technique. However, the findings with either preparation must be verified by similar determinations in the other. We have, therefore, made an extensive study of various digitalis preparations on denervated heart-lung preparations from both normal and previously digitalized dogs, supplemented by a large number of experiments on intact dogs. While we fully appreciate the fact that experimental work on normal hearts may give results which are not necessarily

TABLE I

CHANGES IN CORONARY SINUS OUTFLOW AFTER ADMINISTRATION OF SINGLE DOSES OF DIGITALIS BODIES IN DENERVATED HEART-LUNG PREPARATIONS*

DRUG	EARLY				LATE			
	TOTAL ANIMALS	DECREASE	NO CHANGE	INCREASE	DECREASE	NO CHANGE	INCREASE	NO DATA
Nondigitalized animals								
Digalen	5	1	2	2	0	4	0	1
Digifoline	3	3	0	0	0	0	3	0
Digiglusin	3	3	0	0	0	0	2	1
Scillaren	7	7	0	0	0	1	6	0
Strophanthin	7	7	0	0	0	0	6	1
Digitalis Tr.	15	13	2	0	3	3	7	2
Digitalis Tr.†	5	5	0	0	1	1	3	0
Total	45	39 (87%)	4 (8%)	2 (4%)	4 (8%)	9 (20%)	27 (60%)	5 (11%)
Digitalized animals Digiglusin	8	8	0	0	2	0	6	0
Grand Total	53	47 (89%)	4 (8%)	2 (3%)	6 (11%)	9 (17%)	33 (62%)	5 (9%)

*_Early_ refers to first ten-minute period after injection; _late_, to any subsequent change within forty minutes after injection. The column headed _No Data_ includes experiments which are not considered in the Late period because of some change in the experimental condition, e.g., altered respiration, or venous return, etc.

†After atropine.

duplicated in diseased hearts, such experiments do help in determining the action of the drug under investigation, and thus aid in analyzing its true therapeutic value.

METHOD

The members of the digitalis group used in this investigation were bought on the open market, namely, fresh tinctures and digiglusin (Eli Lilly and Company), fresh tinctures (Sharp & Dohme), and ampoules of digalen, digifoline, strophanthin, and scillaren. As in previous studies,[9, 10] we employed the Starling denervated heart-lung preparation as the most satisfactory method of determining the direct effect of these drugs on the coronary vessels. With this preparation all central action is eliminated, blood pressure can be maintained at a relatively constant level, and major variations resulting from changes in carbon dioxide and oxygen concentration are eliminated because of the constancy of artificial respiration. The temperature is maintained by passing the returned blood through a *constant temperature* bath. In both the heart-lung and intact animal preparations, the Morawitz cannula is introduced into the coronary sinus through the right auricle.

RESULTS

A. The Denervated Heart-Lung Preparation.—We determined the effect of a single injection of various members of the digitalis group on the coronary flow of fifty-three dogs (Table I). In forty-seven of these preparations there was a decrease in flow within the first ten-minute period following the injection. This decrease is the most consistent response observed in the heart-lung preparation and was obtained following the administration of all the drugs except digalen.

A small dose of digalen in one preparation caused a slight decrease, in two others, no significant change, and in the remaining two animals, an increase in the coronary flow. These changes occurred during the first ten-minute period following the injection (Table I). Repeated injections of this drug produced a similar response.

Fig. 1 graphically illustrates the average coronary flow and blood pressure in a number of heart-lung preparations for the ten-minute period immediately preceding and for successive ten-minute periods following the injection of the drug tested. The effect of a single injection of strophanthin (*B*), scillaren (*C*), and digitalis tincture, digiglusin and digifoline (*D*) was a decrease in coronary flow shortly after the injection, occurring simultaneously with a rise in blood pressure. This was then followed by an increase in coronary flow, often (*B* and *D*) exceeding the original volume, and by a fall in blood pressure to approximately the initial level. Atropine administered to the animal before the injection of digitalis tincture had no appreciable effect upon the response, as is evident in *E*.

Since there is a possibility that a single dose of 1 or 2 cat units of digitalis tincture might possibly cause constriction in the dog's heart as a toxic manifestation, a number of experiments were carried out in which this amount was divided and injected in equal portions at five-

or ten-minute intervals. Fig. 2*B* illustrates the results of four such experiments in which injections were made at five-minute intervals. Similar results were obtained with this method of administration as with the single dose method. Comparing the curves in Fig. 1 and Fig.

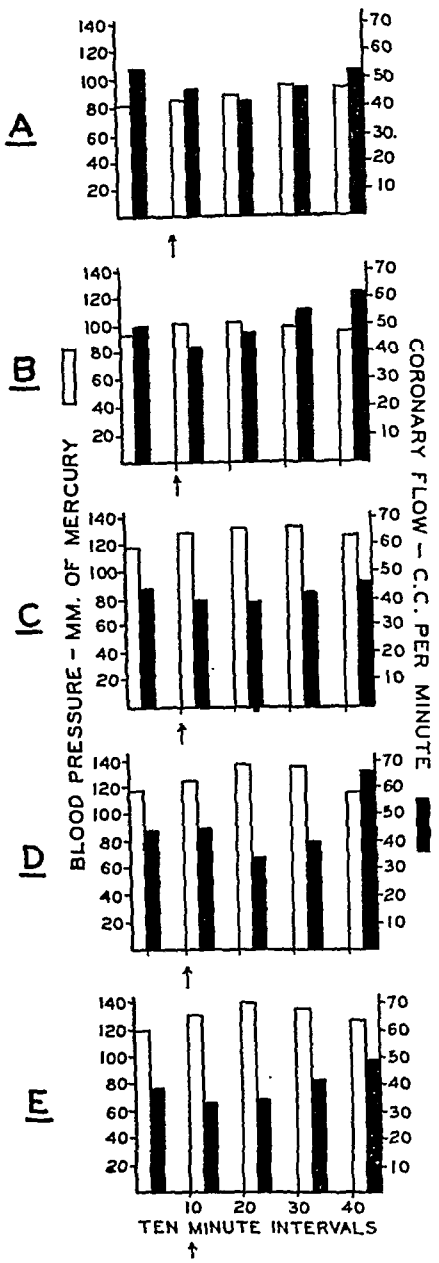

Fig. 1.—The coronary sinus outflow (black) and blood pressure (white) in heart-lung preparations. *A*, Average of results from six digitalized dogs. First column represents preinjection blood pressure and coronary sinus outflow. At arrow, one cat unit of digiglusin was injected into the venous return. Each block represents the average for five-minute periods. *B*, Same as *A* except that the one animal used was not previously digitalized. The blocks represent averages for ten-minute periods. At arrow, ¼ c.c. strophanthin was injected. *C*, Same as *B* except that five nondigitalized animals were used. At arrow, ¼ c.c. scillaren was injected. *D*, Same as *C* except that eight nondigitalized animals were used and at arrow, ½ cat unit (two dogs) or two cat units (six dogs) of tincture of digitalis was injected. *E*, Same as *D* except that the five preparations used were atropinized before the injection of tincture of digitalis (one cat unit).

2*B*, one can see that the constriction which results from the repeated injections of small doses comes on more gradually than after a single dose. The increase in coronary flow begins approximately at the same time in both cases.

Since a late increase in coronary flow was so frequent in intact and heart-lung preparations after both single and repeated injections, it seemed desirable to determine what effect, if any, preliminary digitalization of the animal would have on the coronary response to digitalis.

Twenty-six animals were digitalized according to the dosage scheme of Eggleston, as described by Sollmann.[11] The drug was administered intravenously after dilution with saline solution. We have compared the electrocardiographic changes occurring in our intact unanesthetized dogs after digitalis administration with the electrocardiographic changes in fifteen normal human subjects reported by Larsen and his co-workers.[12] These investigators found a lowering of the T-wave, a depression of the S-T interval, and a lengthened Q-T interval in most of their subjects. The electrocardiographic changes which we obtained in dogs, following the administration of digitalis in comparable therapeutic doses, were essentially the same as those described by Larsen and therefore were considered to be indicative of complete digitalization. Additional investigations are now in progress to determine the electrocardiographic changes following digitalization.

Of these twenty-six digitalized animals, eight were used as denervated heart-lung preparations. The data recorded in Table I and Fig. 1*A* show that the injection of a single cat unit of digiglusin caused a consistent fall in the coronary flow shortly after the injection and a rise in coronary flow later in the experiment. The blood pressure did not fall during the later periods of the experiment (compare with 1*D*) but remained fairly constant at some level usually above the original pressure. During the course of these experiments, it was observed that the digitalized heart is much more sensitive to the mechanical trauma incident to the surgical procedures, necessitating extreme care in preparation. The period required for satisfactory stabilization of coronary flow and blood pressure before injection was frequently much longer than that required for the similar stabilization of a nondigitalized dog.

B. The Intact Animal.—The results obtained when intact animals were used to test the action of the same series of drugs were not so consistent as those in the heart-lung preparations. Of forty-seven such determinations, an early decrease in coronary outflow was recorded in twenty (Table II); in fifteen, there was no significant change; in twelve, there was a definite increase. The number of experiments in which digalen, digifoline and digitalis tincture were administered in single doses to intact animals, as indicated in Table II, seems too small to merit any specific comment on their action. Additional experiments with these

drugs, which, for various reasons, are not included in Table II, yielded results which are similar to our other observations. The response to digalen was the least consistent of all the drugs studied; the results obtained with digifoline and digitalis tincture in the intact animal were essentially the same (Table II). Judging from our results on the intact animal, strophanthin must be considered as causing a definite early coronary constriction in most cases, which is followed by a later increase in outflow.

When the dose of digitalis tincture was divided into equal portions and administered to intact dogs at five-minute intervals, the effect was essentially the same as if administered in a single dose (Figs. 2*A* and

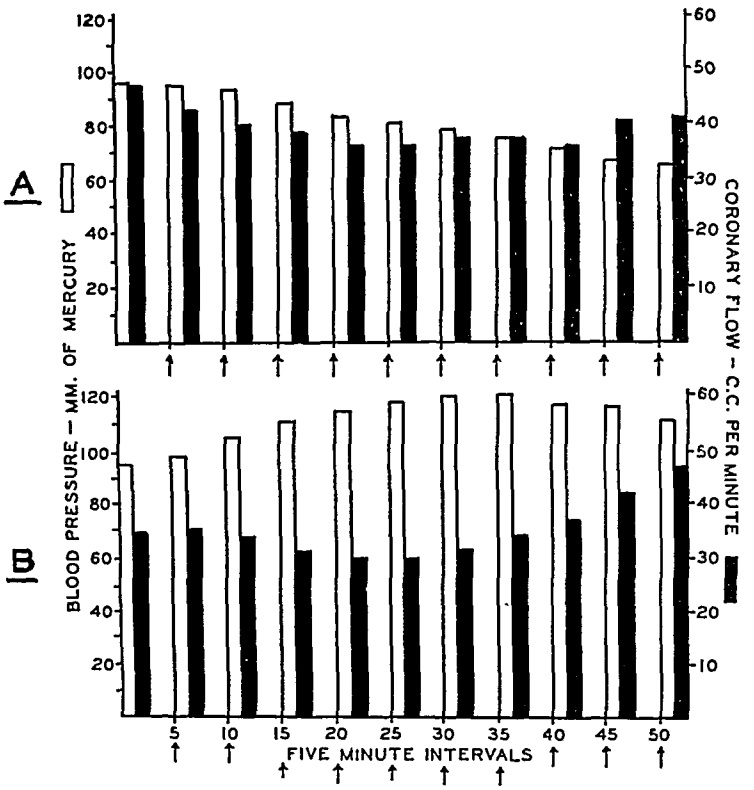

Fig. 2.—The coronary sinus outflow (black) and blood pressure (white) after repeated small injections of digitalis tincture. *A*, Average of the results from four intact dogs. The first column represents the preinjection blood pressure and coronary sinus outflow. Each arrow indicates the injection of 0.1 cat unit of digitalis tincture. *B*, Average of the results from seven heart-lung preparations in which five animals received 0.1 cat unit and two animals received 0.2 cat unit of digitalis tincture at five-minute intervals.

3*A*). In some cases the appearance of the early reduction and later increase in coronary flow were delayed, although this is not evident from Fig. 2*A*.

The modification of the response to digiglusin after preliminary digitalization was striking (Fig. 3*A* and *B*). In nondigitalized animals receiving the first dose of this drug at the time of the experiment, the flow was reduced in only four of twelve animals; there was no change in seven; and there was an increase in one (Table II). Later in the

TABLE II

CHANGES IN CORONARY SINUS OUTFLOW AFTER ADMINISTRATION OF SINGLE DOSES OF DIGITALIS BODIES IN THE INTACT ANIMAL*

DRUG	EARLY				LATE			
	TOTAL ANIMALS	DECREASE	NO CHANGE	INCREASE	DECREASE	NO CHANGE	INCREASE	NO DATA
Nondigitalized animals								
Digalen	1	1	0	0	0	0	1	0
Digifoline	1	0	0	1	0	0	0	1
Digiglusin	12	4	7	1	0	4	7	1
Scillaren	4	1	2	1	0	3	1	0
Strophanthin	9	6	3	0	0	2	6	1
Digitalis Tr.	3	1	0	2	0	0	2	1
Total	30	13 (43%)	12 (40%)	5 (16%)	0 (0%)	9 (30%)	17 (56%)	4 (13%)
Digitalized animals Digiglusin	17	7	3	7	0	2	13	2
Grand Total	47	20 (43%)	15 (32%)	12 (25%)	0 (0%)	11 (23%)	30 (64%)	6 (13%)

*See first footnote, Table I.

experiment, an increase in flow to some point above the original level was recorded in seven animals, while this level was reattained in four animals. In the seventeen animals that were digitalized preliminary to the experiment (Table II), there was a decrease in the coronary outflow in seven, an increase in seven, and no significant change in three. In the later portion of the experiment, thirteen of the seventeen exhibited an increase in flow, which, while not very marked, is very significant in view of the simultaneous decline in blood pressure.

DISCUSSION

The results which we are reporting, i.e., an early decrease followed by an increase in coronary flow after the administration of digitalis, might account for the contradictory conclusions reached by previous investi-

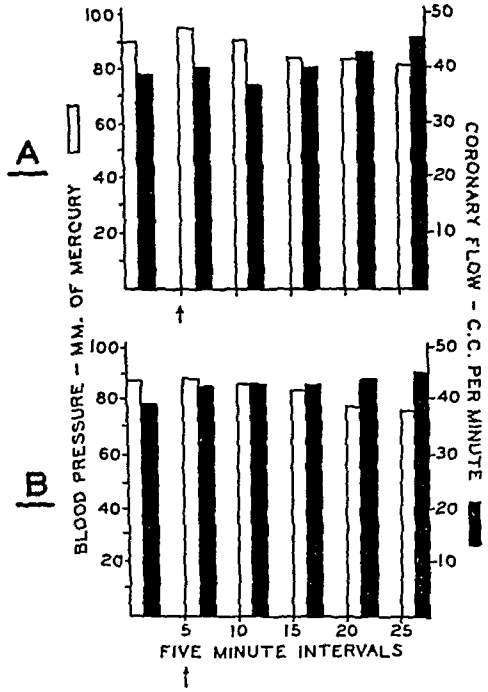

Fig. 3.—The coronary sinus outflow (black) and blood pressure (white) in nondigitalized and digitalized intact animals after a single injection of digiglusin or digifoline. *A*, Average of the results from eight intact nondigitalized dogs. The first column represents the preinjection blood pressure and coronary sinus outflow. The arrow indicates the single injection of 1 c.c. (six dogs), 0.66 c.c. (one dog), or 0.25 c.c. (one dog) of digiglusin or digifoline. *B*, Average of the results from twelve digitalized intact dogs after a single injection of 0.02 c.c. digiglusin per kilogram of body weight.

gators as to the effect of the digitalis bodies on the coronary circulation. If only the early effect of digitalis on the coronary flow is considered, the evidence will be in favor of a reduced flow caused possibly by constriction of the coronary vessels. If only the late effect, i.e., the increased flow which almost always follows this early reduction in both the heart-lung preparation and the intact animal is considered, the conclusion might be either that no significant change in flow had occurred or that the flow was increased. In most of our animals any

detrimental effects of the decrease which occurred during the ten-minute period immediately following the injection might be compensated for by the beneficial effects of the increase during the next period of twenty or more minutes.

In our series of experiments the changes in the coronary blood flow were as consistent in the atropinized heart-lung preparations as they were in the nonatropinized preparations. These results indicate that the alteration in coronary flow after digitalis administration is due to a direct action of the drug on the myocardium or the coronary vessels, rather than on the extrinsic nervous mechanism. These findings are not in agreement with those of Gilbert and Fenn,[7] who found that in either the vagotomized or the atropinized animal there was no decrease in coronary flow which could not be accounted for by the change in blood pressure.

It is possible that the decrease in coronary flow which follows a single injection of digitalis may cause an anoxemia which is responsible for the later dilation of the coronary vessels. While our results on digitalized animals are not strikingly different from those on nondigitalized animals, they do demonstrate that repeated injections of digitalis bodies do not lead to an unfavorable reduction in blood flow through the myocardium; on the contrary, there is a greater tendency to increased flow in the intact animal which has been digitalized. We observed that the hearts of digitalized animals tend to be hypersensitive to experimental manipulations, which often results in a marked irregularity in action or a slower rate of contraction.

Clinical investigations on the tendency of digitalis to increase the frequency of cardiac pains in patients suffering from angina have been reviewed by Fenn and Gilbert.[13] These investigators stated that in some of their patients angina pectoris attacks developed as a result of digitalis treatment. More recently, Gold, et al.,[14] have made an extensive investigation of the severity and frequency of cardiac pain in patients suffering from cardiac disease, none of whom had signs of congestive heart failure. All patients studied had pain on effort. After a course of treatment with digitalis, 15 per cent of their patients reported an increase in pain, while in 30 per cent the pain was diminished. Similar results were obtained during the use of a placebo. On the basis of their results they came to the conclusion that in cases of angina pectoris without congestion there is very little likelihood that the use of digitalis will, by direct action on the circulation, increase or diminish cardiac pain.

This conclusion is not inconsistent with the results we have obtained on dogs. The reduction in coronary flow which we and others have recorded is never of sufficient magnitude to cause much disturbance of cardiac function. The fairly constant increase of coronary blood flow

which follows the initial decrease would soon counteract any unfavorable condition that might have occurred. Since reduction in coronary flow is more marked and more constant in the heart-lung preparation than in the intact animal after digitalis, it seems reasonable to conclude that even if digitalis has a direct constrictor action upon the coronary vessels the other circulatory changes which follow the administration of this drug are such that the coronary flow is not reduced markedly despite the constriction.

The increased coronary blood flow which follows the period of reduced flow is probably the result of the improvement in the general circulation which is caused by digitalis.

SUMMARY

1. The effect of various digitalis preparations on the coronary sinus outflow of heart-lung preparations and intact dogs was studied.

2. In the heart-lung preparations the most consistent effect was a decrease in the coronary flow during a period of about ten minutes. This was, in most cases, followed by an increase in the coronary flow which persisted throughout the remainder of the experimental period.

3. Similar results were obtained in intact animals, but they were not so definite. In many of these animals no appreciable change in the coronary flow occurred; in others, there was a slight increase.

4. In heart-lung preparations from digitalized dogs, the injection of digitalis bodies led to a decrease in coronary flow for about ten minutes. This was followed by an increase which persisted throughout the remainder of the experimental period.

5. In intact digitalized dogs the injection of digitalis bodies produced an increase in the coronary flow which was preceded by very little, if any, decrease.

6. Our results would indicate that the constrictor effect of digitalis upon the coronary circulation is not of sufficient magnitude to contraindicate its use in cardiac disease, except in those cases in which there is a very marked deficiency in coronary circulation.

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THE MEASUREMENT OF VENOUS PRESSURE BY THE DIRECT METHOD*

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VENOUS pressure measurements are accepted as a definite aid in the diagnosis of "right-sided" heart failure. In our experience, however, they have been of relatively little assistance in the diagnosis of the borderline cases of congestive failure in which the use of a quantitative method is particularly important. One of the reasons for the difficulty of interpreting the measurement in any given patient is the degree of variation in the reports of venous pressures in normal people, as illustrated in Tables I and II.

There are in general two factors, aside from individual differences, which may explain this variation in the range of venous pressure in normal people: first, the variety of instrumental methods used; and second, the lack of uniformity in the definition of the "reference point," or the level at which the zero point of the manometer is set. Consideration of the method and the reference point is the purpose of this paper.

There are two related, but slightly different, definitions of peripheral venous pressure. One is concerned with the measurement of the actual pressure existing at a given moment in a given vein; this may be designated as "local" venous pressure. In this measurement the zero point of the manometer is set at the level of the vein itself. Such a measurement is concerned with local phenomena, such as the pressure and flow relationships between the capillaries and the veins to which they lead.

Venous pressure may also be considered in relation to the return of blood to the right auricle, and the measurement of such pressure expressed in terms which take into consideration the position of the right auricle. Pressure so expressed may be influenced by changes in the cardiac function; it may be designed as "general" venous pressure. In addition to the level of the auricle, a factor to be considered in relation to the general venous pressure is the intrathoracic pressure. The pressure influencing flow from extrathoracic veins to the auricle is actually the difference between the "general" (hydrostatic) venous pressure and the intrathoracic pressure. For example, if the pressure

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in the antecubital vein when referred to the level of the auricle is 50 mm. of water and the negative pressure in the thorax is 50 mm. of water then the total pressure influencing the flow of blood to the auricle is 100 mm. of water. This difference is usually referred to as the "effective" venous pressure. Ideally venous pressure should be expressed in terms of the effective pressure, actually the measurement of intrathoracic pressure is not practicable in most cases. The accuracy of the venous pressure determination is therefore handicapped at the start since it is possible that, under particular circumstances, changes in the intrathoracic pressure may affect the level of the pressures in the extrathoracic veins. This discussion will be concerned with what has been defined as "general" venous pressure without corrections for possible fluctuations in the intrathoracic pressure.

The pressure in a superficial vein may be evaluated by three general methods: (1) direct inspection and palpation of the vein; (2) determination of the pressure necessary to collapse the vein, the so-called "indirect" method; and (3) the measurement of the pressure exerted through a needle in the lumen of the vein, the "direct" method. This discussion will be limited to a consideration of the measurement of venous pressure by the direct method.

Though various types of apparatus have been used to measure venous pressure directly, the most widely used and on the whole the most satisfactory instrument is that described by Moritz and von Tabora.[1] This apparatus consists of a system of tubes filled with liquid, similar to that shown in Fig. 1. The manometer tube of this system can obviously be placed at any desired level regardless of the site of venipuncture. Appropriate use of this method permits repeated readings over considerable periods of time with a single venipuncture. In these studies the only modifications in the apparatus of Moritz and von Tabora were the addition of a side arm syringe and the substitution of normal saline for the citrate solution. Except for special observations, which will be designated, all measurements were made with the subject in the supine position.

In an attempt to evaluate the potential sources of error in the apparatus, consideration was given to the bore of the manometer, the size of the needles, and the length of the tubing. It is clear that in any method involving the measurement of pressure by the height of a fluid level in a small bore manometer, a source of error is introduced by the capillarity of the manometer tube. Manometers of 1 mm. bore, such as the usual spinal fluid manometer, have a capillarity (with water) of roughly 25 mm., whereas one of 2 mm. bore has a capillarity of roughly 12 mm. In larger tubing the capillarity is sufficiently small to be of no significance in venous pressure measurements. Throughout these studies a manometer of 2 mm. bore was used, which implies an error of 12 mm. in all reported readings.

Within the limits of gauge 14 to gauge 25 (inside diameter approximately 0.25 to 1.5 mm.), the size of the needle through which the pressure is measured imposes no error on the final pressure recorded, but influences the time required before a constant level is attained. Also, when the smaller needles are used, the system is less sensitive in reflecting minor changes in pressure, such as those observed in different phases of the cardiac or respiratory cycles.

No important errors were produced by minor variations in the length of the tubing. It is important, as in all methods using fluid in tubing, to be sure that air bubbles have been eliminated.

There is no agreement among observers as to the optimum position of the arm when the antecubital vein is used for the measurement of

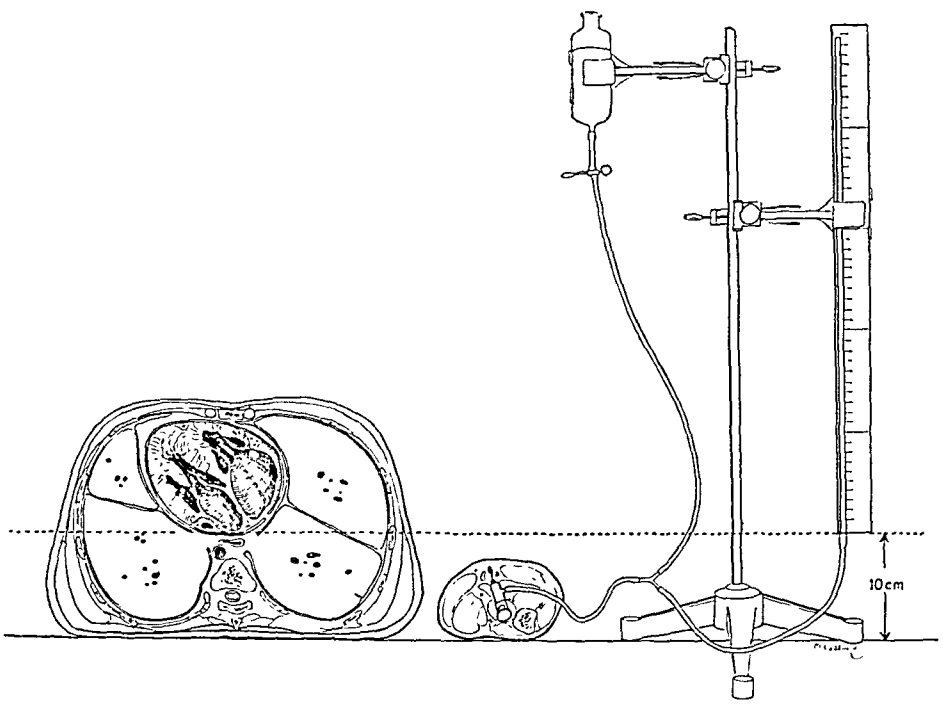

Fig. 1.—Apparatus for the measurement of venous pressure.

the venous pressure. Accordingly, this question was studied by observing the influence on the venous pressure readings of changes in the level of the elbow, in the degree of abduction of the shoulder, and in the supination or pronation of the forearm.

It is a common observation that when the arm is raised above the level of the heart the veins collapse. It has been demonstrated by Carrier and Rehberg[2] and by von Recklinghausen[3] that, when the hand is raised from below the heart level upward and the point of reference kept constant, the pressure in the veins in the dorsum of the hand decreases nearly proportionately to the decrease in the hydrostatic pressure. However, when the pressure in the antecubital vein is measured by the direct method as described, with the ante-

cubital vein at various positions above or below the assumed heart level, there is a different series of events. In 20 subjects in the supine position the pressure in the antecubital vein remained essentially unchanged when the elbow was raised or lowered, as long as it was not raised above a critical level near the center of the chest. The exact position of this level varied considerably in different individuals, but when the elbow was raised above it the pressure in the antecubital vein tended to *rise*. In general, the higher the site of venipuncture was raised above this level the greater was the increase in the venous pressure. Examples of these results are shown in Fig. 2. This eleva-

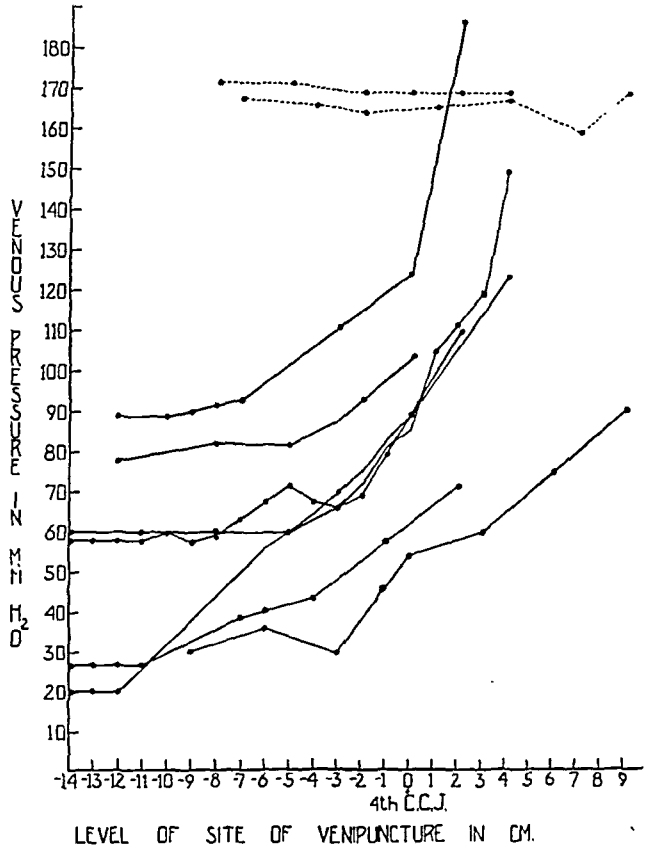

Fig. 2.—Change of venous pressure with elevation of site of venipuncture. Venous pressure measured with the zero point of the manometer 5 cm. posterior to the fourth costochondral junction. The dotted lines represent two patients with heart failure. In this chart the abbreviation "C.C.J." refers to the costochondral junction.

tion of the venous pressure with change in the level of the site of venipuncture was not due to a change in the height of the column of blood in the distal veins because passive flexion of the elbow with elevation of the hand and forearm above the site of venipuncture did not change the pressure in the antecubital vein.

When this same procedure was applied to subjects with elevated venous pressure, no comparable change occurred, as is also shown in Fig. 2. This may suggest that the apparent increase in venous pressure in normal subjects was the result of (or was influenced by) a

collapse of the vein at some point between the site of venipuncture and the auricle—a collapse which does not occur under these circumstances in patients with sufficiently elevated venous pressures.

To evaluate the effect, if any, of abduction of the shoulder on the venous pressure, readings were made at 10-, 45- and 90-degree abduction. In a fair majority of cases the venous pressure varied slightly with changes in the abduction of the shoulder. Ten-degree abduction frequently gave slightly higher readings than 45-degree abduction. At 90-degree abduction the venous pressure was usually the same as at 45 degrees, but occasionally elevations of considerable magnitude would occur. In general, the lowest readings were obtained with 45-degree abduction.

Pronation and supination of the forearm made no difference in the venous pressure in most of the cases studied. A position of relaxation and comfort was more important than the degree of rotation of the forearm.

Certain variations in the physiologic state of the individual, such as muscular exertion, muscle tension, emotional tension, changes in the type of respiration, pain, and variations in the environmental temperature were also considered as possible distorting influences on the venous pressure.

It is well known that exercise is accompanied by an elevation in venous pressure.[4, 5, 6, 7, 8] The degree of this elevation and the time required for the venous pressure to return to a constant level after exertion depend on the extent of the exercise and on the functional capacity of the circulation in the individual. In patients with heart failure exertion is said to produce a greater elevation in venous pressure and one that lasts over a considerably longer time than in normal subjects. Consequently, the time required for the attainment of "standard" conditions with regard to venous pressure will vary with the degree of exertion just before the test, the ability of the subject to relax, and the state of the circulation. In normal subjects working about the laboratory, from four to eight minutes were required after cessation of activity before a constant venous pressure reading was reached.

Tension of groups of muscles caused no appreciable change in the venous pressure unless it directly affected the venous flow from the needle to the thorax. Movements of the thoracic muscles or arm muscles proximal to the site of venipuncture often caused a rise in the venous pressure. Movement of the diaphragm exerted a marked influence on the venous pressure, and minor activity, such as talking, appeared to distort the venous pressure, presumably through changes in the intrathoracic pressure.

Similar to the effects of muscular tension and perhaps related to them were those of emotional tension. Often in highly nervous sub-

jects the venous pressure readings were variable until adequate relaxation was obtained. The breathing of such subjects was at times quite irregular, which may in part explain transient changes in the venous pressure.

Frequently during continuous observations on relaxed subjects a drop in venous pressure of 5 to 40 mm. occurred directly following an unusually deep or sighing respiration. Falsely low readings may be recorded as a result of such transient fluctuations unless the respirations are carefully watched and the venous pressure is followed for several minutes.

In normal subjects an increase in the rate of respirations, shallow or deep, is accompanied by a fall in the venous pressure.[9, 10] In our observations this fall began at the onset of abnormal breathing, and the venous pressure tended to be maintained at the new low level until normal respirations were resumed. Holding the breath was accompanied by a rise in the venous pressure. Marked variations in pressure occurred with resisted expiratory effort from the inspiratory position of the chest (Valsalva experiment) and resisted inspiratory effort from the expiratory position of the chest (Müller experiment).

The pain that is occasionally elicited by venipuncture caused no definite effect on the venous pressure unless the subject tensed the diaphragm or other muscles. Discomfort is best avoided by the use of novocain at the site of venipuncture.

When heat dissipation remained unimpaired, variation in the environmental temperature within fairly wide limits (45 to 100° F.) had no effect on the venous pressure. When the temperature was so low that shivering occurred, there was a moderate rise in the venous pressure. Artificial fever, according to the work of Gibson and Kopp,[11] causes a considerable elevation of venous pressure when it is associated with capillary dilatation.

In a few individuals sudden transient increases in the venous pressure occurred during the test without any apparent external cause and when the subjects were conscious of no subjective changes. Venous spasm has been suggested to explain such changes, but in none of our cases was this directly observed.

In general, repeated readings in the same individual over several months, using the precautions outlined above, have shown little variation in the level of venous pressure. In a few patients, however, especially those who have difficulty in relaxing, variations of the order of 20 to 30 mm. occurred.

One of the most important elements in the technique of venous pressure measurement is the selection of the reference point, or the level at which the zero point of the manometer is set. There is no unanimity of opinion among observers as to the exact position of this point. Some have defined the level they use with accuracy; others

have indicated only that the zero point of the manometer should be set at "the level of the right auricle." It may be said that there is general agreement in the literature that the reference point should be at the level of the auricle, but there is considerable variety of opinion as to the location of this point in a given subject. This has led to the use of reference points which may vary from one another by as much as 50 mm., with a corresponding variation imposed on the venous pressure reading.

Three definitions of the reference point for the supine position have been used more frequently than others. Von Recklinghausen[3] defined the level of what he termed the venous reservoir as the midpoint of the thorax. Moritz and von Tabora[1] defined the level of the right auricle as 5 cm. dorsal to the fourth costochondral junction. Eyster[12] used the junction of the middle and anterior thirds of the thoracic diameter as the level of the reference point. Tables I and II list the reference points used by various authors in their studies of venous pressures in normal persons.

The suitability of these reference points has been tested by three sets of studies. First, post-mortem material and anatomical specimens have been examined to establish the location of the auricle in the thoracic cage. Second, in 42 normal subjects the apparent position of the auricle was determined by fluoroscopy and the venous pressure was measured in relation to the reference point so selected. Third, on the assumption that variation in the position of the reference point is a factor in the width of the range of venous pressure observed in normal people, a study of the various reference points in relation to this range has been made.

The results of these studies may now be considered. The position of the right auricle in its relationship to the front and back of the chest was studied in cross sections of 14 cadavers. These bodies had been frozen in the supine position, and the section had passed through the chest at the level of the tricuspid valve. In each of these specimens the posterior border of the right auricle was between 80 and 105 mm. anterior to the skin of the back. This measurement was from 40 to 50 per cent of the thoracic diameter. The most posterior portion of the heart at this level was usually the right auricle. The auricle itself measured from 40 to 70 mm. in anteroposterior diameter, and the anterior border was usually within 40 to 50 mm. of the anterior border of the thorax. These findings, and certain observations made at autopsies, led to the attempt to use the posterior border of the cardiac shadow in the fluoroscope (with the subject in the supine position) as an approximation to the level of the right auricle.

Using the precautions described in the first portion of this paper, the venous pressure was measured in 42 normal subjects in the supine position. With the fluoroscope the level of the posterior border of

the heart was then estimated with the subjects in the same position on the same table.* In these subjects the posterior border of the heart shadow lay from 65 to 100 mm. anterior to the skin of the back (35 to 55 per cent of the thoracic diameter). This is not very differ-

TABLE I

VENOUS PRESSURES OF NORMAL PERSONS BY DIRECT METHODS

DATE	AUTHOR	POSITION OF PATIENT	REFERENCE POINT	RANGE
	A. Saline-Filled System, e.g., Moritz and von Tabora			*mm. saline*
1910	Moritz and von Tabora[1]	Supine	5 cm. posterior to the 4th costochondral junction	10-90
1910	von Tabora[14]	Supine		80-120
1912	Schott[4]	Supine		44-130
1912	Frank and Reh[15]	Supine		10-60
1920	Arnoldi[16]	Supine		77-103
1920	Moog and Ehrmann[17]	Supine		Below 100
1921	Fuchs[18]	Supine		15-125
1922	Kroetz[19]	Supine		0-70
1924	Boas and Dooneief[20]	Supine		10-100
1924	Runge[21]	Supine	4th costochondral junction	48-60
1927	Blumgart and Weiss[22]	Supine	5 cm. posterior to the 4th costochondral junction	25-50
1928	Harris[23]	Supine	Anterior axillary line	50-75 25-150
1930	Ernst and Stagelschmidt[24]	Supine	5 cm. posterior to the 4th costochondral junction	Below 120
1930	Gönczy, Kiss, and Enyedy	Supine		55-112
1931	Brandt[27]	Supine		50-100
1932	Criep[27]	Supine		Average 102
1933	Brams, Katz, and Schutz[28]	Supine	Junction of anterior and middle thirds of thoracic diameter	45-135
1933	Harrison[29]	Supine	5 cm. posterior to the 4th costochondral junction	50-65
		Sitting	Level of right auricle	50-100
1934	Budelmann[30]	Supine	5 cm. posterior to the 4th costochondral junction	34-72
1934	Griffith, Chamberlain, and Kitchell[31]	Supine	2½ in. dorsal to angle of Louis	60-120
1935	Overholt and Pilcher[32]	Supine		Below 120
1935	Wood, Capaccio, and Weaver[33]	Supine	5 cm. posterior to the 4th costochondral junction	65-105
1935	Wartman[34]	Supine		60-120
1936	Krinsky and Gottlieb[9]	Supine		Average 11.8
1937	Ferris and Wilkins[35]	Supine		40-100
	B. Air-Filled System With Aneroid Manometer			*mm. water*
1914	Claude, Porak, and Rouillard[36]	Supine	----------	*80-240*
1921	Villaret, Saint-Girons, and Jacquemin-Guillaume[37]	Supine	----------	Below 130 ♂ Below 120 ♀
1922	Leconte and Yacoel[38]	Supine	----------	140 ♂ 120 ♀
1923	Castellotti[39]	Supine	----------	40-70
1923	Corradi[40]	Supine	----------	88-132
1923	Gazzotti[41]	Supine	----------	*140 ♂ 130 ♀*
1924	Bedford and Wright[42]	Supine	10 cm. below sternum at subcostal angle	5-150

*The authors acknowledge with gratitude the expert assistance of Dr. M. C. Sosman and Dr. John Larkin in studying these subjects with the fluoroscope.

TABLE I—CONT'D

DATE	AUTHOR	POSITION OF PATIENT	REFERENCE POINT	RANGE
	C. Blood-Filled System, e.g., L-Tube Method			*mm. blood*
1918	Marris[43]	Supine	----------	40-60
1923	Young[44]	Supine	"8 cm. deep from sternum"	100-140
1930	Taylor, Thomas, and Schleiter[45]	Supine	Midaxillary line	40-100
1932	Evans[46]	Supine	Midaxillary line	75-150
1934	Fishberg, Hitzig, and King[47]	Supine	5 cm. below sternum at 4th rib	40-80
1935	Robertson and Fetter[48]	Upright	"Right auricle"	90-125
1935	Kinsman and Moore[49]	?	?	20-150
1936	Cohen[50]	Supine	Right auricle	60-120
1936	Hussey[51]	Supine	Midaxillary line	40-120
1936	Wood[52]	45° upright	4th intercostal space	20-105
1937	Candel and Rabinowitz[53]	?	?	40-80
1937	Hurst and Brand[54]	?	Vein placed 4-5 cm. below right auricle	50-90
1937	Berger[55]	?	5 cm. below sternum at 4th intercostal space	Average 77
1937	Gibson and Evans[56]	Supine	Midaxillary line	40-130

ent from the observations made on cadavers, but, when these individually determined zero points were used in the measurement of venous pressure, the range of variation was greater than when any of the arbitrary zero points mentioned above was used. This wide variation may be due to the difficulties inherent in this method of establishing the level of the auricle.

The three arbitrary reference points mentioned are similar in that each of them is influenced by the anteroposterior diameter of the thorax. In the group of 42 cases so far considered there was relatively little variation in the size of the chest. The validity of these points was put to a further test by determining the venous pressure in 48 more normal subjects with widely different thoracic diameters. The two groups were combined and the analysis of the venous pressure measurements in these 90 patients is shown in Figs. 3, 4, and 5.

In general, it may be said that, when subjects with widely varying thoracic diameters are studied, there is a wide variation in the range of venous pressure as determined with these standard reference points and that there is a relationship between the size of the chest and the level of the venous pressure. It may even be said that with the use of these reference points, the greater the thoracic diameter the lower the apparent venous pressure tends to be (Fig. 6).

Now there is no reason to believe that individuals with large thoracic diameters should in fact have lower venous pressures than those with smaller chests. Indeed, the work of Kountz and others[13] has suggested that the contrary may be the case. It is therefore sug-

TABLE II

VENOUS PRESSURES OF NORMAL PERSONS BY INDIRECT METHODS

DATE	AUTHOR	POSITION OF PATIENT	METHOD	REFERENCE POINT	RANGE MM. H_2O
1902	Frey[57]	Sitting	Weights on vein to prevent back flow of blood	Hand placed at level of right auricle	10-20 gm.
1902	Von Basch[58]	Sitting	Mercury in glass cylinder	Hand placed at level of right auricle	52-108
1906	Von Recklinghausen[3]	Sitting	Capsule and air	Sternoclavicular joint	20-120
		Supine	Capsule and air	Midway between xiphoid and back	20-120
1906	Sewall[59]	Sitting	Calibrated spring to collapse vein	Level of heart	Average 44
1908	Hooker and Eyster[60]	Sitting	Capsule	Level of heart	40-99
1911	Hooker[61]	Sitting	Capsule	Midway between tip of sternum and back	20-160
1912	Howell[62]	Erect	Pressure at which arm begins to swell	Costal angle	40-130
1913	Barach and Marks[63]	Erect	Capsule	Subcostal angle	80-180
		Horizontal	Capsule	?	35-110
1914	Hooker[64]	Supine	Capsule	Midway between costal angle and back	124-156 day 70-80 night
1915	Clark[65]	At 45° reclining	Capsule	Midway between costal angle and back	50-160
1916	Hooker[66]	At 45° reclining	Capsule	Midway between costal angle and back	190 below 50 yr. 260 above 75 yr.
1918	Brown[67]	Recumbent	Capsule with fluid medium in place of air	Level of heart	30-90
1918	Briscoe[68]	Sitting	Capsule	Subcostal angle	90-120 ♂ 70-110 ♀
1924	White[69]	Sitting	Capsule	Subcostal angle	35-95
1924	Eyster and Middleton[7]	----------	Capsule	----------	10-100
1929	Eyster[12]	Supine	Capsule	Junction of anterior and middle thirds of thoracic diameter	40-60
		Sitting	Capsule	?	40-60
1931	Kastlin and Maclachlan[71]	Horizontal	Capsule and transillumination	Junction of anterior and middle thirds of thoracic diameter	Below 110
1932	Owens[72]	Recumbent	Capsule	?	35-90
		Erect	Capsule	?	Average 90
1932	Kountz, Pearson, and Koenig[13]	Sitting	Capsule with air	Subcostal angle	Below 70
1933	Brams, Katz and Schutz[28]	Horizontal	Capsule and transillumination	Junction of anterior and middle thirds of thoracic diameter	40-135

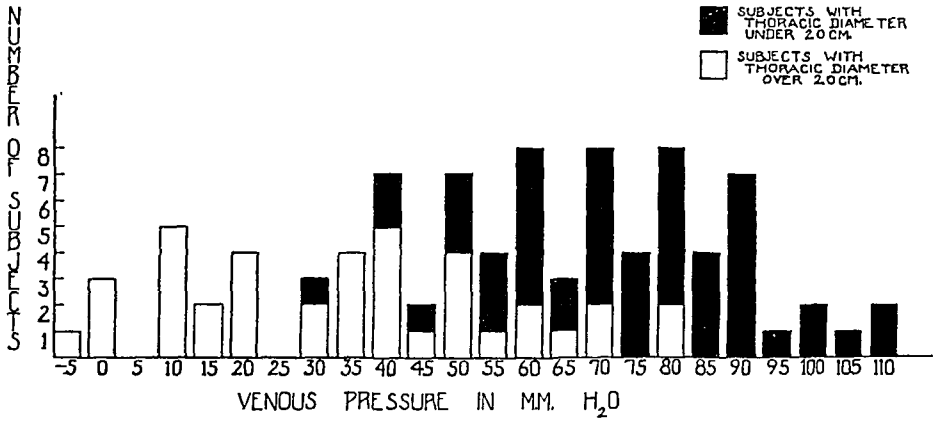

Fig. 3.—Venous pressure measurements in 90 normal subjects using the reference point of Moritz and von Tabora, 5 cm. dorsal to fourth costochondral junction.

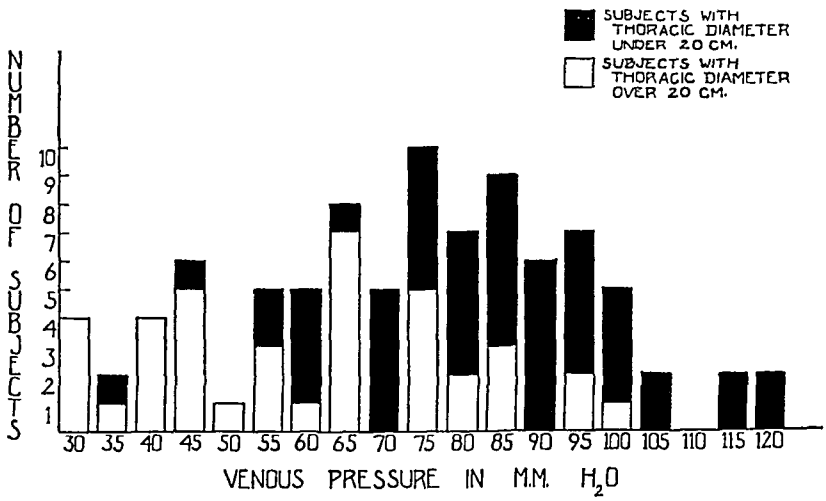

Fig. 4.—Venous pressure measurements in 90 normal subjects using the reference point of Eyster, at junction of middle and anterior thirds of thorax.

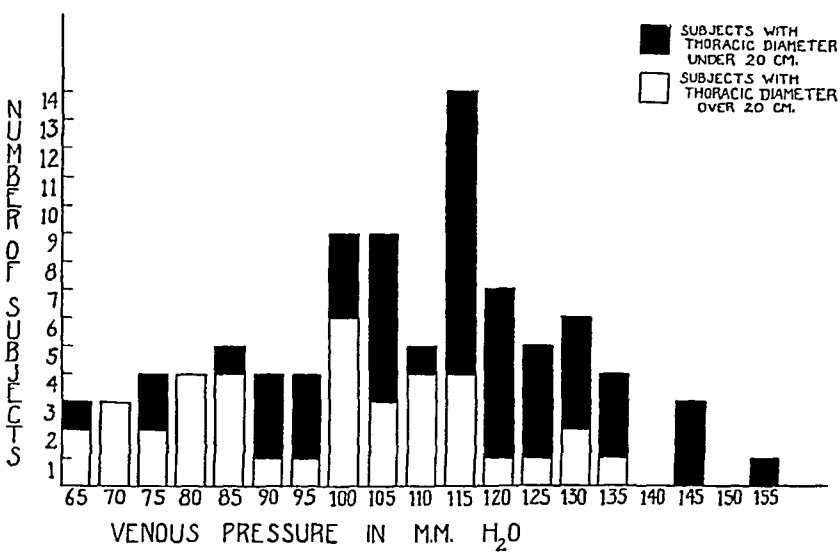

Fig. 5.—Venous pressure measurements in 90 normal subjects using the reference point of von Recklinghausen, at midpoint of thorax.

gested that the venous pressures found in these persons with large chests are low, not because of an actual change in the venous pressure, but because the shape of the thorax has resulted in the setting of the zero point in a falsely high position. After all, there seems to be little reason to relate the level of the venous reservoir to the front of the chest when the subject is in the supine position. It might be expected that the level of the auricle under these conditions would be more closely related to the posterior boundaries of the thorax, on which the heart lies, than to the anterior thoracic wall to which it is not even firmly attached. As seen in these results, the more the element of the thoracic diameter is minimized in the selection of the reference point, the narrower is the range of venous pressure and the more equitable is the distribution about the mean of the subjects with larger chests.

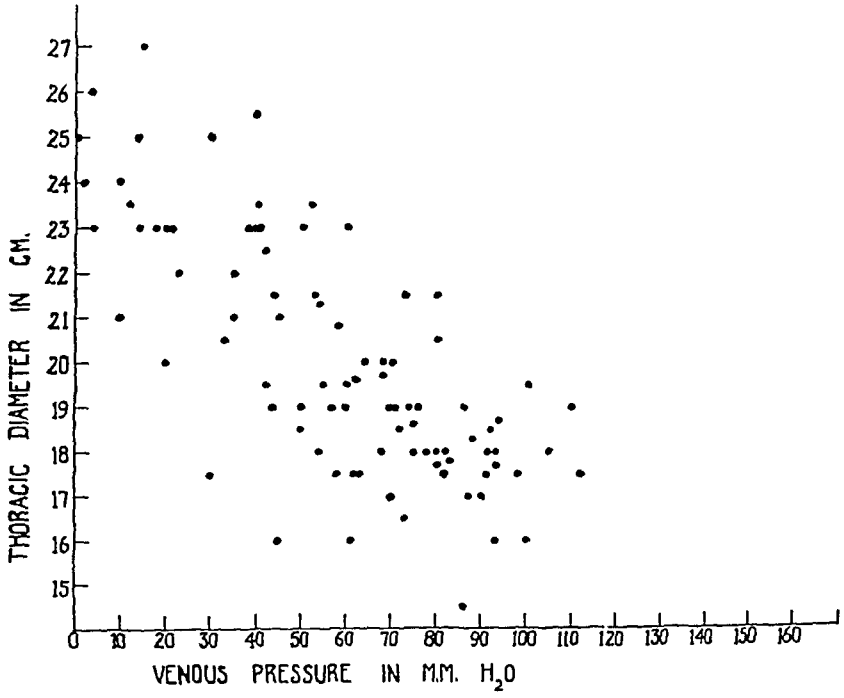

Fig. 6.—Venous pressure in relation to thoracic diameter in 90 normal subjects using the reference point of Moritz and von Tabora.

These considerations led us to eliminate the thoracic diameter in the establishment of the reference point by placing the zero point of the manometer in a constant relation to the level of the table on which the subject was lying. For reasons to be discussed later the point chosen was 100 mm. above the table. When this point was used, approximately 80 per cent of the subjects had venous pressures falling within a 60 mm. range, and there was an equal distribution of the subjects with large chests on each side of the mean pressure (Fig. 7).

The use of a point related to the back of the thorax as a reference point has added to the usefulness of the venous pressure measurement in patients with large chests who showed evidence of mild right-sided

heart failure. With the use of the Moritz and von Tabora reference point, venous pressure measurements in such cases gave values only at the upper limits of normal, but, with the use of a point related to the back of the thorax, the venous pressures were definitely elevated and more nearly in accord with the state of the patient.

In view of the above findings it is suggested that an acceptable reference point should be defined in relation to the posterior surface of the chest rather than in relation to the thoracic diameter or the anterior surface of the chest. To approximate the level of the right auricle, it is suggested that the reference point be set 100 mm. above the skin of the back, i.e., 100 mm. above the table top. This 100 mm. is about the distance from the back to the posterior border of the auricle in the frozen sections of cadavers (see Fig. 1); the distance also compares with the rougher measurements obtained with the aid

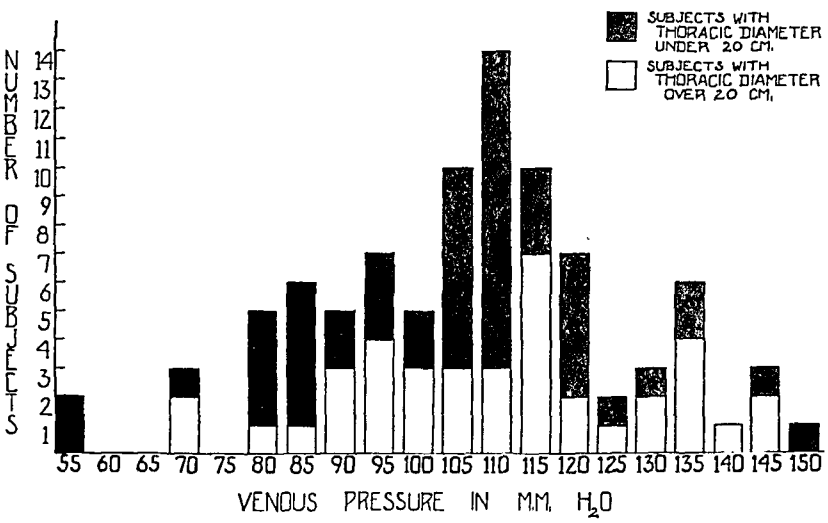

Fig. 7.—Venous pressure measurements in 90 normal subjects with the reference point in a constant relation to the level of the table—100 mm. anterior to back of thorax.

of the fluoroscope. When this reference point was used, the extreme range of venous pressure of 90 normal subjects was from 50 to 150 mm.; 80 per cent of the readings lay between 80 and 130 mm. This reference point of course is for use only when the subject is in the supine position.*

*Since venous pressure measurements are often desired in patients with severe cardiac failure who are unable to lie flat, an attempt was made to compare venous pressure in the supine position with the pressure in the 45-degree reclining and 90-degree sitting positions. In the upright positions the reference point and the site of venipuncture were placed at the level of the fourth costochondral junction. Fifty normal subjects were studied in this manner. The range of venous pressure is from 20 to 105 mm. in the 45-degree reclining position and from 40 to 135 mm. in the 90-degree position. These ranges are not very different from those observed in the supine position, but in a given individual there was no apparent relation between the level of venous pressure in one position and that in the other. The lack of relation was marked in some patients with heart failure who had abnormally high venous pressures in the supine position but often had venous pressures within the presumed normal range in the upright positions. Because of the absence of relationship between the venous pressure in the supine and upright position in normal subjects and the disparity in the venous pressure levels in these positions in cases with congestion, it seems, in the present state of our knowledge, that measurements of venous pressure in different positions of the body cannot be directly compared.

Figs. 8 and 9 are presented to show the position of the reference point in cross sections of two chests of different diameters. In Fig. 8 the anteroposterior diameter of the thorax is 17 cm. In a chest of such size the position of the reference point is satisfactorily established near the level of the right auricle when either the point 5 cm. posterior to the fourth costochondral junction or that 100 mm. an-

Fig. 8.

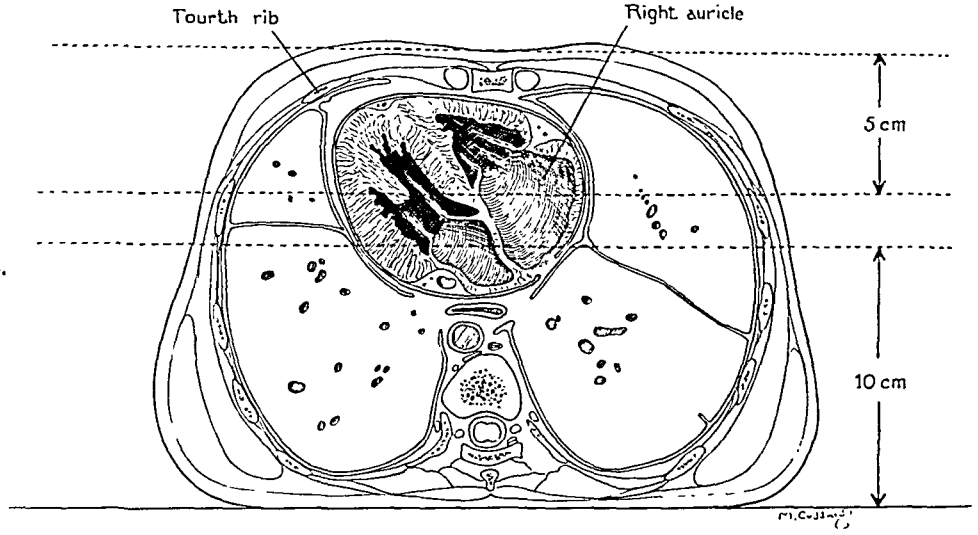

Fig. 9.

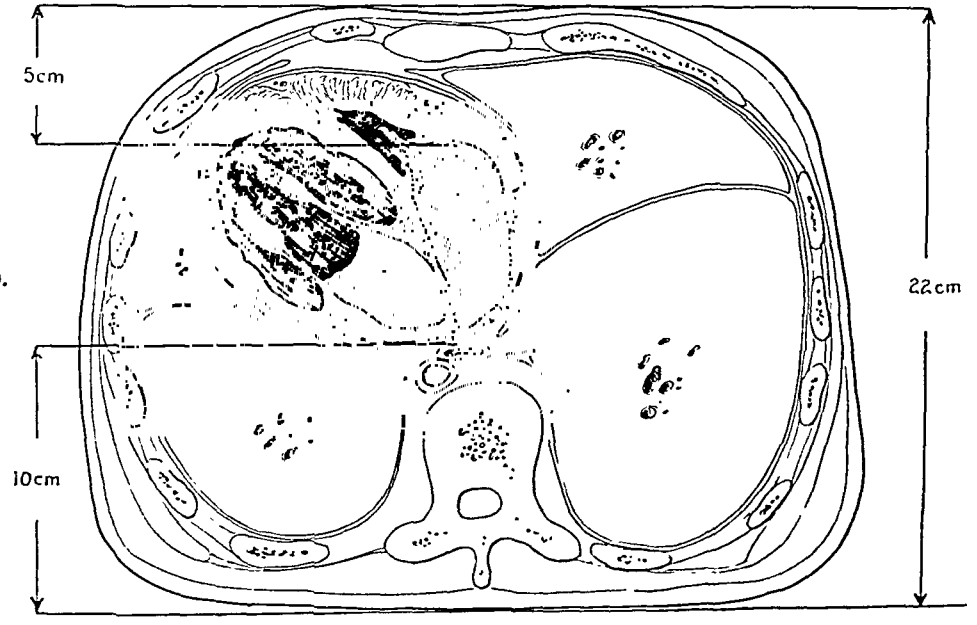

Fig. 8.—Cross section of cadaver redrawn from Eycleshymer and Schoemaker. Thoracic diameter, 17 cm. With this thoracic diameter all the reference points in common use are near the level of the right auricle.

Fig. 9.—Cross section of cadaver. Thoracic diameter 22 cm. With this thoracic diameter the level of the reference point of Moritz and von Tabora is at the upper border of the right auricle.

terior to the top of the table is used. In chests of larger size, as in Fig. 9, the reference point 5 cm. posterior to the fourth costochondral junction is in a less constant relation to the auricle than when a point

100 mm. anterior to the back is used. The observations under the fluoroscope and on cadavers indicate that in adults the thickness of the vertebrae and other structures posterior to the heart is less variable than the thoracic diameter in the same patients. This observation is the basis for the selection of the reference point 100 mm. anterior to the back of the chest. It is to be expected that in young children the bony structure is so much smaller that a different reference point will be required. No attempt has been made to study this aspect of the problem.

The usefulness of a reference point which is not displaced by variations in the thoracic diameter is illustrated by Fig. 10. This is a lateral view of the chest of an emphysematous patient in the supine

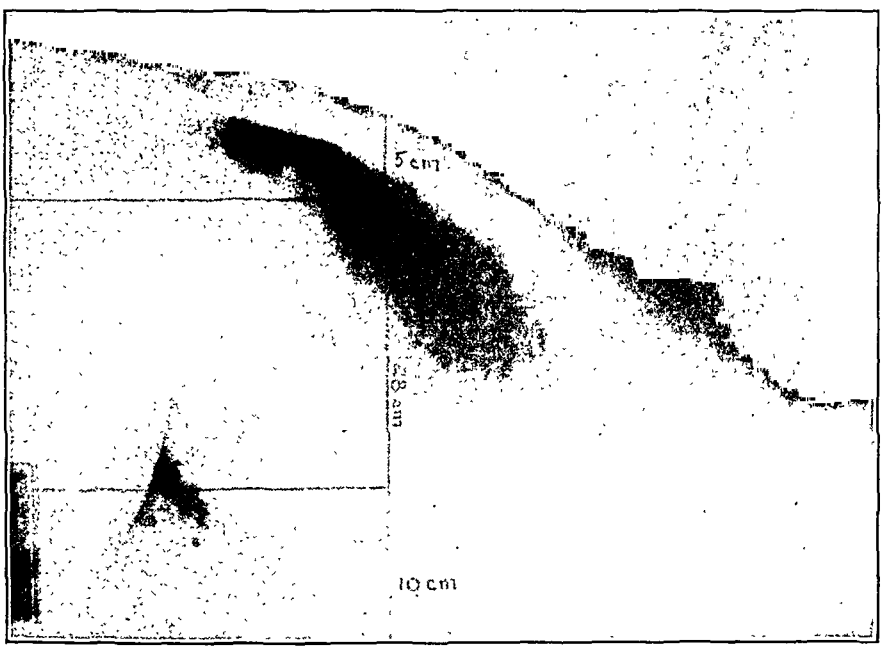

Fig. 10.—Lateral view of subject in supine position. The thoracic diameter at the fourth costochondral junction is 28 cm. This illustrates the failure of the reference point of Moritz and von Tabora to approximate the level of the auricle in subjects with deep chests.

position. The anteroposterior thoracic diameter was 28 cm. The reference point of Moritz and von Tabora places the zero point of the manometer at or near the level of the apex of the heart. On the other hand, a level 100 mm. above the table top closely expresses the position of the right auricle. In such an individual the venous pressure as measured by the method of Moritz and von Tabora could be elevated at least 130 mm. before it reached an abnormal value.

TECHNIQUE SUGGESTED FOR MEASUREMENT OF VENOUS PRESSURE

On the basis of the observations here reported, a standard modification of the Moritz and von Tabora method of measuring venous pressure is suggested, as follows: The apparatus of Moritz and von

Tabora is used, selecting manometer tubing of 2 mm. bore and a needle of gauge 16 to 20. The subject lies quiet and relaxed in the supine position for ten minutes or more before the measurement is attempted. The arm (the measurement is made in an antecubital vein) is abducted to 45 degrees and supported comfortably on a pillow so that the site of venipuncture is below the level at which the veins tend to collapse (this is usually about the middle of the chest; presumably in subjects with thick chests it may be nearer the back). The zero point of the manometer should be set 100 mm. above the level of the back, i.e., 100 mm. above the table on which the patient lies (Fig. 1).

A tourniquet may be used to facilitate entry into the vein. When the needle enters the vein, the tourniquet is released and salt solution is run into the vein to wash the syringe and needle free of blood. Repeated readings are then made of the level of the fluid in the manometer over a period of several minutes until an essentially constant level of pressure is attained.

SUMMARY

The observations reported in this paper have dealt with some of the factors influencing the measurement of venous pressure by the direct method. They indicate that errors may be introduced (a) by certain variations in the technique, including:

(1) the level of the site of venipuncture, and
(2) the degree of abduction of the arm;

and (b) by certain variations in the state of the patient, including his position, relaxation, and type of respiration. Modifications of current techniques are suggested which tend to minimize these errors.

Moreover, the evidence from anatomical material and from roentgenologic measurements indicates that the methods now used for establishing the level of the auricle may, in persons with deep chests, tend to place the assumed level of the auricle at a falsely high position. This, in turn, leads to a falsely low venous pressure reading. To minimize this error a new method of establishing the reference point is suggested, a method which relates this point to the posterior rather than the anterior surface of the chest. Anatomical evidence indicates that in adults in the supine position the level of the auricle is approximately 100 mm. anterior to the skin of the back. When this level is used as the reference point, variations in chest diameter are not reflected in the venous pressure readings.

The range of venous pressures in normal people in the supine position, using a reference point 100 mm. anterior to the skin of the back, is from 50 to 150 mm. of water.

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UNUSUAL FORMS OF RHYTHMS INVOLVING THE A-V NODE*

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PERSISTENT auriculoventricular rhythm is a rare condition and usually is diagnosed only by means of the electrocardiograph. A survey by Dr. H. A. Kaplan has shown that there were only twenty-four cases in the last 7000 patients' records in our files. Nodal escape and temporary shifting of the pacemaker to the A-V node have been noted to be more common than permanent nodal rhythm. In the past two years we have seen four cases of atrioventricular rhythm which are unusual.

I. RECIPROCAL RHYTHM FOLLOWING STIMULATION OF THE CAROTID SINUS

Although reciprocal rhythm has been described on numerous occasions[1-13] and ascribed to vagal hypertonicity,[9-10] we know of no recorded instance in which it was produced by reflex stimulation, and in which the differentiation from the closely resembling condition of sinus bradycardia, nodal escape, and interference dissociation[14-19] could be made in the same patient. This we have been able to demonstrate in the case which we are reporting. This patient suffered from dizziness, fainting spells, and epileptiform convulsions which could be reproduced by carotid sinus pressure, indicating a hypersensitive carotid sinus mechanism. This was further substantiated by the fact that atropine sulfate relieved the spontaneous attacks and prevented the attacks following carotid sinus compression.

Electrocardiograms (Lead II) taken during carotid sinus pressure (left side) showed on one occasion (Fig. 1) the development of sinus bradycardia (with a shifting pacemaker), a series of nodal escapes, interference dissociation, and once ($R_{10} - P_8 - R_{11}$) a pseudoreciprocal rhythm. On another occasion (Fig. 2) carotid sinus pressure (of both sinuses simultaneously) produced sinus bradycardia, a series of nodal escapes with some retrograde P-waves (P_5, P_6, P_8, P_{19}, P_{20} and P_{21}), and true reciprocal rhythm ($R_6 - P_6 - R_7$, $R_{21} - P_{19} - R_{22}$, and $R_{23} - P_{20} - R_{24}$).

Analyzing Fig. 1 in more detail, it will be seen that following carotid sinus pressure there occurs a shift in the pacemaker (P_5) associated with a prolongation of the P-R interval from 0.16 to 0.20 second, followed by escape of the A-V node with sinus beats interspersed. The QRST complexes of the nodal beats differ in contour from those of the

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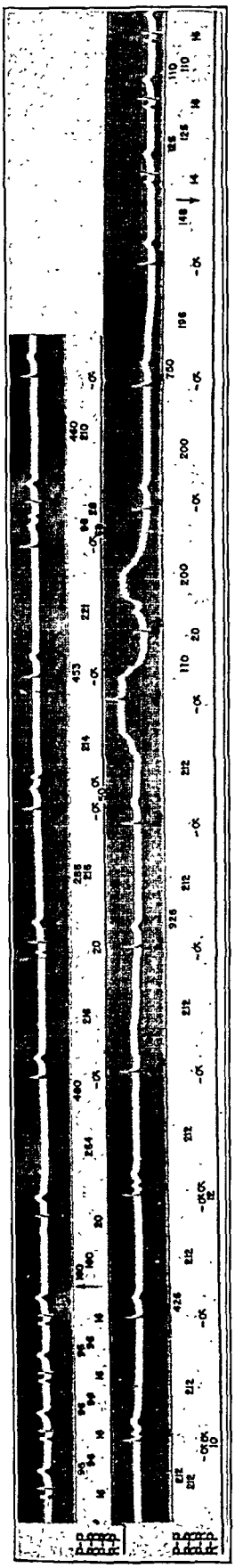

Fig. 1.—Continuous electrocardiographic record (Lead II) showing effect of pressure on left carotid sinus begun at upright arrow and ended at inverted arrow. All the P- and R-waves are labelled sequentially; below the curve are given the R-R, P-P, P-R and in some beats the R-P intervals in 100 times their value in seconds. α and $-\alpha$, respectively, indicate absence of A-V conduction from auricle to ventricle and vice versa. Discussed in text. In Figs. 1 and 2 the reduction in reproduction may make it advisable to use a hand lens.

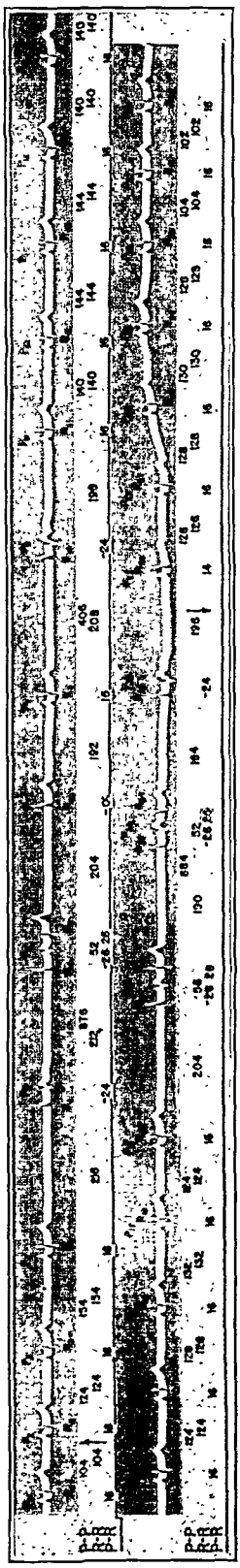

Fig. 2.—Continuous electrocardiographic record (Lead II) showing effect of pressure on both carotid sinuses begun at upright arrow and ended at inverted arrow. Conventions as in Fig. 1. Discussed in text.

sinus beats and differ slightly from each other. As the carotid sinus pressure is continued, the rate of the nodal pacemaker accelerates, i.e., the first nodal escape, R_6, comes after an R-R interval of 2.64 seconds, and the last (R_{23}) before the carotid sinus compression was relaxed occurred after an R-R interval of 1.96. During this period of nodal beats sinus P-waves are seen (e.g., P_6, P_7, P_8, P_9, P_{10}, and P_{11}), some of which are conducted and interrupt the nodal rhythm (e.g., P_6, P_8, and P_{11}); the others are blocked, presumably because they reached the node during its absolute refractory period, i.e., at intervals of 0.50 second, or less, after the nodal beat. P_8, however, occurs 0.68 second after the nodal beat R_{10} and is conducted, simulating reciprocal rhythm. That this is not reciprocal rhythm is shown by the resemblance of P_8 to the other sinus P-waves.[6, 20] In this instance there is retrograde conduction block, as no nodal beat has invaded the auricle.[6, 8, 21]

The conditions illustrated in Fig. 2 are entirely different. Here, carotid sinus pressure causes a slowing of the rate of discharge of the sinus node, e.g., P_3, P_4, P_7, P_9 to P_{18}, P_{22} to P_{26}. Whenever the slowing of the sinus node becomes excessive, as between P_4 and P_7, between P_7 and P_9, and between P_{18} and P_{22}, the A-V node escapes. The nodal beats differ from those shown in Fig. 1, except only R_8, in that there is retrograde conduction giving rise to P-waves (e.g., P_6, P_8, P_{19}, P_{20}, P_{21}) totally different in contour from the sinus P-waves. The R-P intervals of these retrograde P-waves vary from 0.28 second to 0.24 second. In every instance in which the R-P interval is longer than 0.24 second the retrograde P is conducted back through the A-V node, giving rise to a second ventricular complex. However, the retrograde P-waves having an R-P interval of 0.24 second are not conducted back into the ventricle. Apparently the path for auriculoventricular conduction in this instance is refractory when the R-P interval is 0.24 second, but not when the intervals are longer. It is interesting to note that the second ventricular complex of the reciprocal rhythm shows varying degrees of aberrant conduction.

This experience serves to emphasize the fact that reciprocal rhythm should be sharply differentiated from "pseudoreciprocal" rhythm, which resembles it closely, but which is a phenomenon of interference dissociation. Reciprocal rhythm should be diagnosed only when the P-wave between the two ventricular beats differs considerably from the sinus P-waves.[6, 20] This has not always been done in the past. This mechanism is of little practical significance, but it is important in demonstrating the possibility of two-way conduction in quick succession through the A-V node. This is doubtless due to the fact that the path for forward conduction is not the same as that for retrograde conduction. In a dense meshwork of fibers such as occurs in the A-V node, this functional split into more than one conducting path is not difficult

to conceive.[22] The rarity of reciprocal rhythm even when compared to retrograde conduction shows that this split in conduction pathways is unusual indeed. Reciprocal rhythm is one example of the re-entry phenomenon.

II. VARIATIONS IN P-R INTERVALS IN NODAL RHYTHM

In the case of reciprocal rhythm described above there were variations in the R-P interval. Recently, we have seen two other somewhat similar cases (Figs. 3 and 4). In both it will be noted that the R-R interval is constant, while the R-P or P-R interval varies and with it the P-P interval. There are two possibilities to consider in such cases:

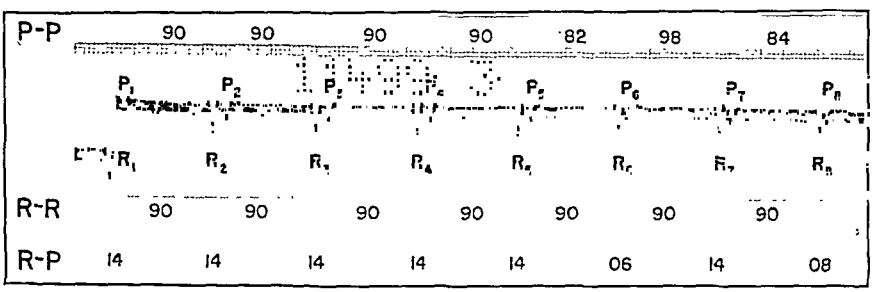

Fig. 3.—Electrocardiographic record (Lead III) showing variations in P-R interval in a case of nodal rhythm. Since in all the beats R precedes P, the P-R interval is given as R-P. Conventions otherwise as in Fig. 1. Discussed in text.

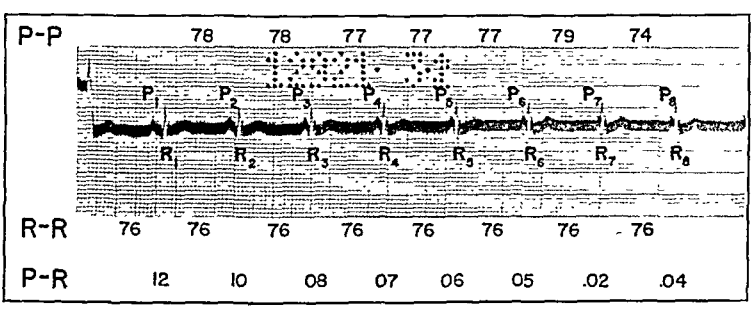

Fig. 4.—Electrocardiographic record (Lead II) showing variation in P-R interval in a case of nodal rhythm. Conventions as in Fig. 1. Discussed in text.

(1) a shift in the nodal pacemaker or (2) variation in the retrograde conduction. In these cases we are inclined to the view that the variability of the P-R (R-P) interval is due to the second mechanism, since there are no variations in the R-R intervals such as would be expected if the former were true. It is well known that forward conduction through the A-V node occurs with greater facility than retrograde conduction, and it is therefore understandable that the latter will be more susceptible of variation than the former. The possibility that we are dealing with sinus arrhythmia and simultaneous nodal rhythm with interference dissociation is ruled out, we believe, by the fact that in both of these patients the other leads show nodal rhythm with constant P-R (R-P) intervals.

III. SHORT P-R INTERVAL ASSOCIATED WITH LENGTHENED QRS INTERVAL

A number of reports have appeared dealing with records of short P-R intervals associated with lengthening of the QRS interval.[23-27] It was concluded that this condition is more benign than other forms of intraventricular block and is probably not a sign of heart disease. While Wolf, Parkinson, and White[24] ascribed it to functional intraventricular block due to abnormal spread through the junctional conducting tissue and ventricles, Wolferth and Wood[23] attribute the phenomenon to early arrival of the impulse to the ventricle via the bundle of Kent

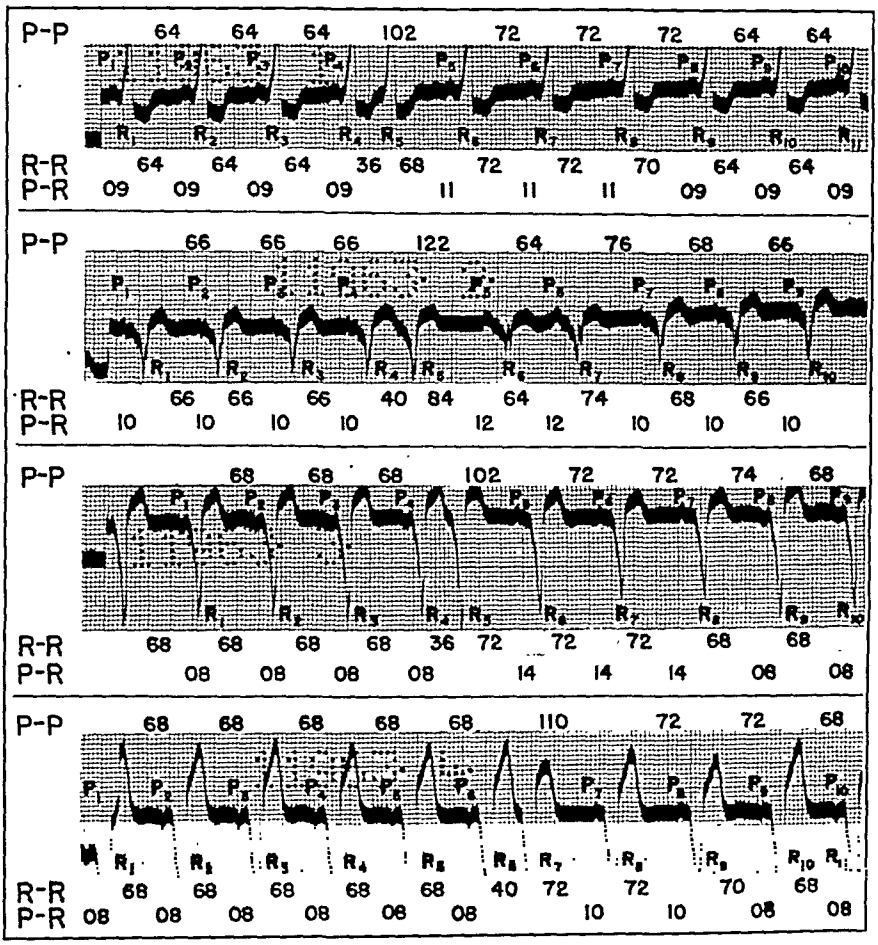

Fig. 5.—Electrocardiographic record (all four leads; fourth lead is CF_2 American Heart Association classification) showing an unusual instance of transient shortening of P-R interval in a case of organic intraventricular block. Conventions as in Fig. 1. Discussed in text.

(located at the junction between right auricle and ventricle), thereby making the spread through the ventricles abnormal. In many cases the disappearance of the condition spontaneously or with atropinization causes the P-R interval to lengthen as the QRS interval shortens. However, this was not true in one of Tung's cases.[26] We have recently seen an instance of short P-R interval and long QRS interval in a patient with severe cardiac damage caused by coronary sclerosis. In this patient ventricular premature systoles caused changes in the P-R interval without abolishing the intraventricular block. The record is shown in Fig.

5. The change in the P-wave contour and in the P-R interval following the extrasystoles is readily seen (as well as the associated change in QRS contour). The interpretation in this case, we believe, is of intraventricular block of the common bundle branch variety associated with an upper nodal rhythm, reverting at times to the sinus node or to another focus in the A-V node. The intraventricular block is persistent regardless of where the impulse arises, and in this case has the same prognostic significance as intraventricular block with normal P-R intervals. It is difficult to conceive that, in this case, we are dealing with spread through the bundle of Kent, and consequently we question this interpretation in other instances. It is possible to produce a shift in the pacemaker to the A-V node with a consequent shortening of P-R interval either when the sinus node is diseased or depressed by vagus stimulation. Under such circumstances it is conceivable that the impulse may spread through a preferential path[25] in the junctional conduction tissue since the disease affecting the sinus node, or the vagal depression, may also affect the A-V junctional tissue. Aberrant conduction is not uncommon in nodal escape, and it is highly probable that this may on occasion be severe enough to simulate organic intraventricular block. When the pacemaker reverts to the sinus node the spread through the ventricles may become normal again or, as in our case, may persist. It is unnecessary in view of these circumstances to postulate spread over the hypothetic bundle of Kent. In upper nodal rhythm it has been shown[15, 28, 29, 30] that the P-wave often does not differ remarkably from the sinus P since the auricular spread in both is of a similar pattern, the only difference being the shortened P-R interval.

SUMMARY

Several unusual electrocardiograms illustrating different forms of A-V rhythm have been described:

1. A case in which, with carotid sinus hyperirritability and reflex stimulation, the differentiation of reciprocal rhythm and the closely resembling condition of sinus bradycardia, nodal escape and interference dissociation with pseudoreciprocal rhythm could be demonstrated.

2. Two electrocardiograms which showed variations in the P-R (R-P) interval, but in which the R-R interval remained constant.

3. One electrocardiogram which showed a short P-R interval and a prolonged QRS complex, with a shift in the pacemaker to the S-A node following an ectopic ventricular beat, from a patient with severe chronic cardiac disease.

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CORONARY OCCLUSION, HEART FAILURE, AND ENVIRONMENTAL TEMPERATURES*

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CINCINNATI, OHIO

RECENT discussion concerning seasonal variation in the frequency of attacks of coronary occlusion has emphasized the need for more complete knowledge of the relation of environmental temperatures to coronary thrombosis and heart failure. There has been a feeling that the increased frequency of acute infections during winter largely accounts for the higher heart failure and cardiac death rates of that season. Infections, particularly of the respiratory tract, undoubtedly do enter into the increased winter hazards for patients of limited cardiac capacity. But there seem to be, we believe, other important factors at work, factors of a general metabolic nature not usually taken into consideration by cardiologists.

There is in the medical literature no careful study of the onset of noninfectious cardiac failure of various kinds which was made to ascertain whether there be any seasonal fluctuation of statistical significance. For these reasons we have undertaken the study of the problem along two lines of approach. First, we have obtained from the literature reports of large series of cases of coronary occlusion which included information as to the months in which the acute attacks occurred. This has been supplemented by material from the autopsy records in this hospital. Second, we have studied the seasonal factor in the records of all patients with noninfectious cardiac failure who were admitted to the Cincinnati General Hospital from Jan. 1, 1920, through Dec. 31, 1937.

CORONARY OCCLUSIONS AND SEASON

Recognition of the clinical entity of coronary thrombosis and infarction of the heart has become so widespread in the last two decades that adequate data may be collected from the medical literature to ascertain whether any relationship exists between season and acute attacks. Therefore, we have studied published reports with information on this subject and autopsy cases occurring in the Cincinnati General Hospital from 1922 through 1936.

The first reference to any relationship between season and acute attacks of coronary thrombosis appeared in a paper by Wolff and White,[1] in 1926, in which they observed that "most of the cases of coronary thrombosis in New England occur in the winter." Acute coronary

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occlusion in all but one of their twenty-three autopsy cases occurred between October and April, inclusive. The next report was that of Wood and Hedley,[2] in 1935, who found a low summer and high winter incidence in 133 cases in Philadelphia between 1932 and 1934, inclusive. Their series included both private and ward patients. Mullins,[3] in Pittsburgh, analyzed 400 consecutive cases from private, consultation, and hospital practice between July, 1928, and July, 1935. In the 370 in which the date of onset was known, he observed that "almost twice as many initial attacks occurred during December, January, and February, as occurred during the summer months."

By far the largest series was recently reported by Masters, Dack and Jaffe,[4] who collected 612 cases from private, hospital, and consultation practice. Although they noted a higher incidence in December and January, they did not believe that season was important in determining the incidence of acute attacks. This conclusion has been questioned, however, by Rosahn,[5] who used their statistics. Later in the same year one of us[6] reported that in 247 autopsy cases from the Boston City Hospital between 1906 and 1936 there was a low incidence of acute attacks in the summer months. There was a slightly larger number in the spring than the winter.

The time of onset of acute attacks in patients coming to autopsy in the Cincinnati General Hospital from 1922 through 1936 could be ascertained in 278 instances in 8,673 consecutive autopsy records. A number of records were rejected because of lack of information regarding the time of onset. The data as to month of onset of these 278 attacks are included in Fig. 1 and Table I, and reveal the same decline from winter to summer as is seen in all the other observations reported.

TABLE I

DISTRIBUTION BY MONTHS OF ACUTE ATTACKS OF CORONARY OCCLUSION

	JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	TOTAL
Master (New York City)	75	43	48	48	56	44	54	50	46	46	39	63	612
Mullins (Pittsburgh)	36	50	31	28	27	29	24	18	26	29	37	35	370
Present series (Cincinnati)	33	27	25	22	23	13	19	10	22	25	33	26	278
Bean (Boston)	20	18	26	29	20	13	11	11	28	19	25	27	247
Wood and Hedley (Philadelphia)	19	13	8	7	11	1	7	4	15	14	19	15	133
Total	183	151	138	134	137	100	115	93	137	133	163	166	1640

In order to make a comparison of these five groups the number of acute attacks by month was corrected on the basis of a thirty-one-day month. The equalized curves of incidence are found in Fig. 1, in which the percentage of each group occurring month by month is

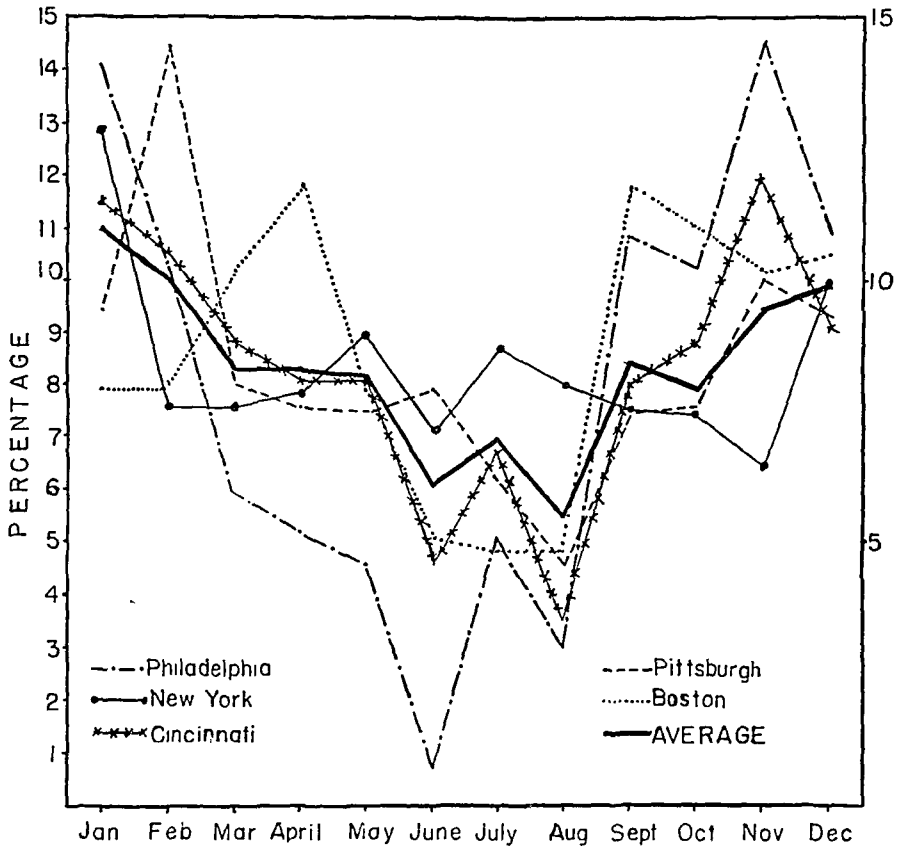

Fig. 1.—Percentage of attacks of coronary occlusion by month corrected on the basis of a thirty-one-day month.

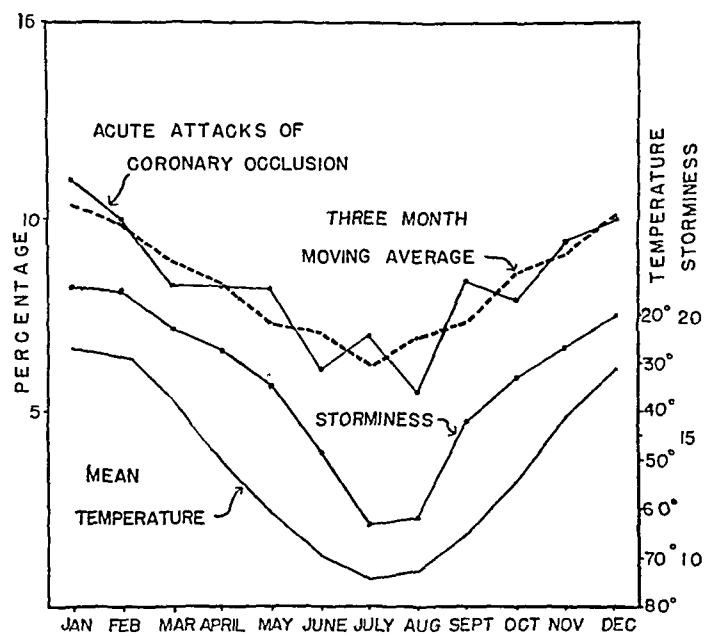

Fig. 2.—Percentage of attacks of coronary occlusion by month compared with mean temperature and storminess.

indicated. The heavy line was obtained by using the entire 1,640 cases, also corrected on the basis of a thirty-one-day month. There is here a high winter and low summer level in the curves from each of these cities. From Table I it can be seen that in January 183 acute attacks occurred, whereas in August there were 93, approximately half of that number. This leaves no doubt that in the regions studied acute episodes of coronary occlusion are considerably more frequent in the winter than in the summer months.

Such chance factors as seasonal variation in population shifts or hospital admissions have been considered negligible in the autopsy material, and because of the different sources of the data we do not believe such factors to be significant.

In Fig. 2 the curve for seasonal incidence of acute attacks has been compared with the mean temperature curve (inverted) and storminess.* The similarity of these curves is at once apparent and strongly suggests that fluctuations in temperature and storminess are related to the events culminating in acute coronary thrombosis.

SEASONAL AND PERIODIC ANNUAL VARIATIONS IN FREQUENCY OF NONINFECTIOUS HEART FAILURE

We next present the picture of noninfectious heart failure in its seasonal variations at Cincinnati. Examination was made of all case records of cardiac patients admitted to the Cincinnati General Hospital from Jan. 1, 1920, to Dec. 31, 1937, and selection made of only those patients admitted in evident heart failure not complicated by infection or other external precipitating events such as injuries, burns, or operations. Cases were included when there was constant edema of the ankles or breathlessness at rest sufficiently severe to incapacitate the patients. Although the degree of failure must have varied, the great majority of the patients admitted were acutely ill. Cases in which failure was initiated or accompanied by acute infection of any kind were discarded, as were those in which the oral temperature was over 100° F. on admission, even though localizing signs of infection were not always found. Records of patients hospitalized within the previous three months were discarded in order to include only those whose heart failure was new. Therefore, those included in our presentation represent, as nearly as we were able to ascertain, patients in whom none of the usually encountered external precipitating causes of cardiac failure were present.

Table II presents the detailed grouping of the onsets and admissions on a seasonal basis, separated according to the organic basis of failure. In the arteriosclerotic group we have included all cases of coronary artery disease, hypertension, or both. A few patients in whom the

*By storminess is meant the day to day changeableness of the temperature, as represented in Figure 4 by mathematical coefficients of variability.

organic basis of the failure was uncertain were included in the group with arteriosclerotic heart disease. By syphilitic heart disease we mean that type associated with aortitis and aortic regurgitation. Adjustment to a thirty-one-day monthly basis was made and three-month moving averages were used in order to bring out clearly the seasonal trends shown in Fig. 3. Arteriosclerotic failure *admissions* to the hospital reach a peak in March, while *onsets* of these failures are highest in

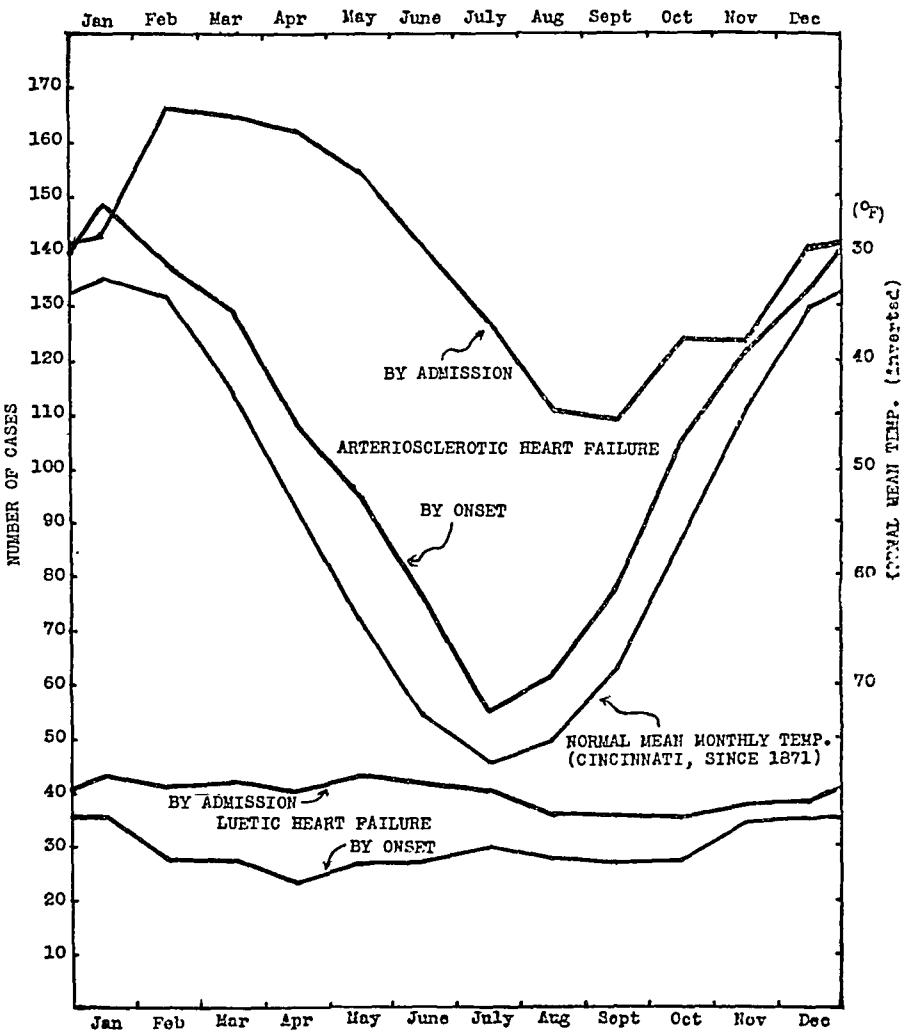

Fig. 3.—Seasonal variation in frequency of heart failure. Actual number of cases equalized to thirty-one-day month basis, smoothed by use of three-month moving average.

February; with the low point of summer a similar one-month lag in admissions is seen. The exceedingly close parallelism between the smoothed onset curve and inverted mean temperature curve for Cincinnati cannot but be of great significance in considerations of the seasonal timing of the failures.

Presumably inactive rheumatic heart disease unaccompanied by fever shows this same seasonal trend in month of onset of congestive failure.

TABLE II

HEART FAILURE ADMISSIONS TO CINCINNATI GENERAL HOSPITAL, 1920-1937, INCLUSIVE (CASES LIMITED AS DESCRIBED IN TEXT)

MONTH	ARTERIOSCLEROTIC			SYPHILITIC			RHEUMATIC	NORMAL
	ACTUAL NO. FAILURES	31-DAY MONTH BASIS	3-MO. MOVING AVERAGE	ACTUAL NO. FAILURES	31-DAY MONTH BASIS	3-MONTH MOVING AVERAGE	ACTUAL NO. FAILURES	MEAN MONTHLY TEMPERATURE CINCINNATI
Failure Onsets by Month								
January	132	132	148	27	27	35.7	13	32.5° F.
February	157	172	137	27	30	27.7	12	34.2° F.
March	108	108	129	26	26	27.3	17	43.1° F.
April	105	108	108	25	26	23.3	5	53.7° F.
May	107	107	95	18	18	26.3	14	64.0° F.
June	67	69	76	34	35	27.0	10	73.0° F.
July	53	53	55	28	28	29.7	9	77.1° F.
August	42	42	61	26	26	27.3	11	75.1° F.
September	89	89	77	27	28	26.3	11	68.8° F.
October	101	101	105	25	25	26.7	20	56.8° F.
November	120	124	121	26	27	34.0	26	44.6° F.
December	139	139	132	50	50	34.7	22	35.1° F.
Failure Admissions by Month								
January	159	159	143	37	37	43.2	23	
February	140	154	166	46	50	41.2	15	
March	186	186	165	36	36	42.3	24	
April	149	154	162	39	40	40.1	22	
May	145	145	155	44	44	42.9	16	
June	162	167	141	43	44	41.8	21	
July	112	112	127	37	37	40.1	13	
August	103	103	111	39	39	36.0	24	
September	115	119	109	31	32	35.7	23	
October	106	106	123	36	36	34.3	23	
November	140	145	123	34	35	37.7	19	
December	117	117	140	42	42	38.0	26	

Although the number of cases is small, we see in Table II that 104 occurred during the colder half of the year, and only 60 during the warmer six months. Syphilitic heart disease, however, shows only a very slight seasonal trend in congestive failure onset, and no significant trend in time of admission.

The seasonal curve of arteriosclerotic heart failure persists if cases be grouped by either race or sex, and is thus a quite general finding. Failures in this group occurred at considerably earlier ages in the colored than in the white race, and slightly earlier in women than in men, but the seasonal relationships of failure onset remain uniform in all groups.

On quite a different basis the decline in frequency of heart failure with rising warmth stands out from our study. Whole years of warmth, particularly when the warmth came in winter months, have been associated with an even sharper drop in frequency of nonsyphilitic heart failure than has the summer period of each year. Fig. 4 shows the striking fall in failure frequency in the arteriosclerotic and rheumatic groups that came with the prolonged period of record warmth beginning late in 1929. The number of failures in syphilitic heart disease again failed to decrease with this warmth, just as they failed to decline in the summer season.

During the period covered by our data (1920-1937, inclusive), total admissions to the medical service and heart failures of the type we have selected increased along roughly parallel courses except during the pronounced and prolonged warmth that began late in 1929. With this world-wide warmth, arteriosclerotic and rheumatic heart failure admissions dropped sharply, while no significant change occurred in the syphilitic rate. The abrupt high peak in failures in the arteriosclerotic group for 1933 may be due in part to the sudden work load placed on the relief population, from which a large share of the hospital admissions come, by the substitution of Civil Works Administration work relief for the previous direct food and cash dole. Some histories of our cardiac patients for that period record that the functional breakdown occurred shortly after the patient went to work.

Probably of more importance is the fact that during the years 1930, 1931, and 1932, the greater part of the annual excess warmth came to ameliorate winter cold. The winters of 1930-31, 1931-32, and 1932-33 were unusually mild and without storms, with shrubs and flowers blooming throughout the winter. From the summer of 1933 on, however, the winters returned more nearly to their normal level of temperature and storminess, while the excess warmth came largely in the summer seasons. Again in the first quarter of 1937, however, marked unseasonal warmth and calm lessened the severity of that winter. This may well have been an important factor in the unusually good health that pre-

vailed during and subsequent to the flood period and may have been somewhat responsible for the sharp reduction in both total and heart failure admissions to the hospital in 1937.

Another contributing factor of considerable importance in accounting for the reduction in arteriosclerotic and rheumatic heart failures from late in 1929 to the beginning of 1933 may well have been the reduced physical work load on the unemployed. From 1933 on, as work relief largely supplanted direct dole, heart failures resumed more nearly their former proportion of total admissions. If the load of physical labor were of paramount importance in determining heart

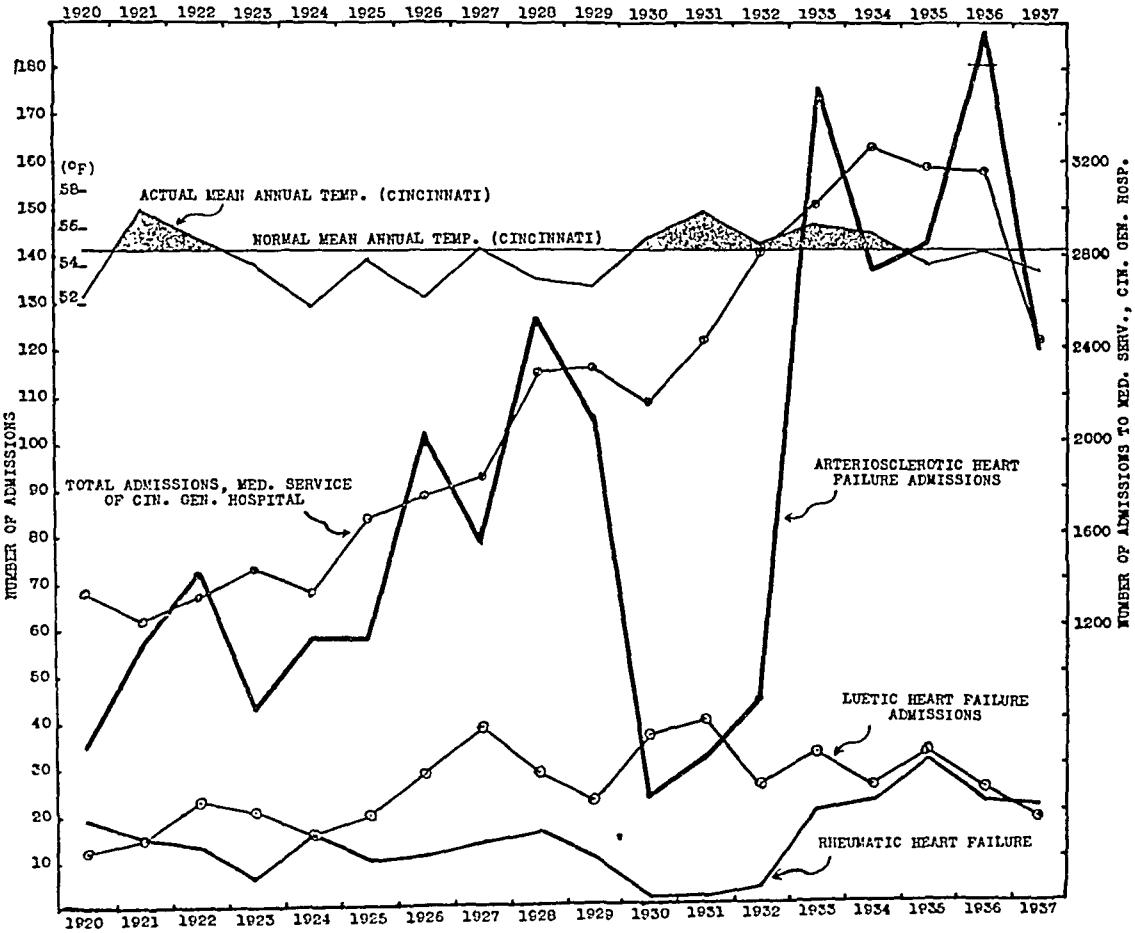

Fig. 4.—Variations in annual frequency of heart failure in relation to mean temperature level.

failure, however, failure admissions should have declined more gradually from 1929 to 1933 as employment lessened. Instead, they declined abruptly as the unseasonable warmth came late in 1929.

Little can be said of the brief warm period of 1921-22. Only with the single winter of 1920-21 did the warmth come to relieve the cold of the winter season, and in only one month was this winter warmth accompanied by any marked reduction in storminess. In addition, this period of warmth came while the influenza epidemic of 1918-19 was still considerably in evidence as a factor in cardiac failure.

Several other factors not investigated by us may have been of some importance in accounting for the fluctuations in admissions for failure. Annual irregularities may well have resulted from changes in personnel of the receiving department. It is also remotely possible, although highly improbable, that other hospitals of the city may have admitted greater numbers of patients with heart failure from the indigent population in the period from 1930 to 1932 inclusive, when so few came to the General Hospital. The only other hospital we considered worthy of checking on this point was the Chronic Disease Hospital at the County Home. This hospital was opened late in 1929, before which time inmates of the County Home had been sent to the General Hospital for cardiac failure. In no year since it opened have more than 20 noninfectious heart failure patients in the arteriosclerotic group, or more than 4 in the syphilitic group been admitted, and there was only one patient with rheumatic heart disease in the nine-year period. The yearly average was 8.2 for the arteriosclerotic and 1.6 for the syphilitic groups. The admissions for heart failure were low in both hospitals concomitantly. Thus the opening of the Chronic Disease Hospital did not account for the low admission frequency in 1930-32 at the General Hospital.

Still another factor which might have affected the annual number of patients with heart failure admitted to the hospital has been variations in the number of cardiac patients cared for in the outpatient clinics. The total number of patient visits to the heart clinics each year, however, does not furnish a likely basis for explaining the sudden drop in failure frequency from late 1929 to early 1933. The only interruption in the steady rise of heart clinic visits during the whole period occurred during the warmth of the early depression years, when hospital admissions for heart failure fell off so sharply. And again in 1937 both clinic visits and admissions for failure fell off together. We may, therefore, disregard the outpatient heart clinic activities.

The fact that syphilitic heart disease was not found to be affected significantly by either seasonal or annual warmth is an interesting commentary on this type of heart failure. Here the progress of the incapacitating lesion seems more rapid than with the arteriosclerotic type, so that the slow effects of season are less evident. Many of the case records of syphilitic heart failure showed that there had been repeated admissions at intervals of less than three months, so that only the initial attack is found in our data. The syphilitic process, from first break in compensation to death, usually took about two years, while most of the arteriosclerotic patients carried on considerably longer. Little stress can be placed on the rheumatic heart failure data because of the small number of acceptable cases. Only with their sharp drop in incidence during the warmth of 1929 to 1933 do they provide information of value.

DISCUSSION

The data presented show a marked seasonal swing in the frequency of coronary occlusion attacks. They are almost twice as frequent in winter as in summer. An even greater winter peak is found in the

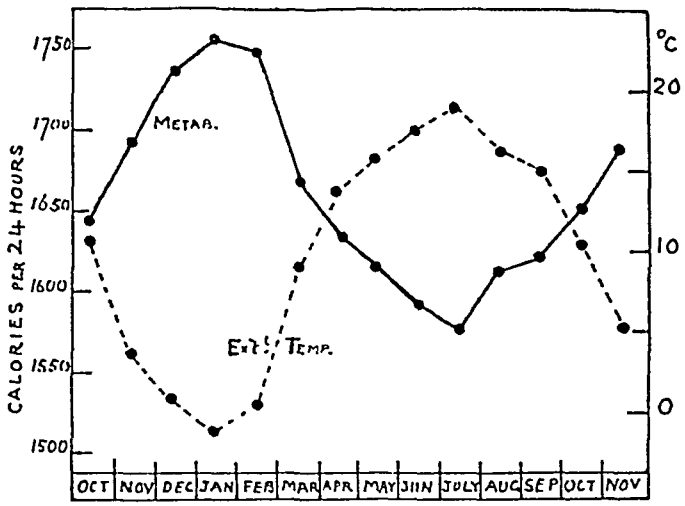

Fig. 5.—Mean monthly metabolism and mean monthly temperature. Gessler (1925), observations on himself. (From Martin, C. J.: Thermal Adjustments of Man and Animals to External Conditions, Lancet 2: 617, 1930.)

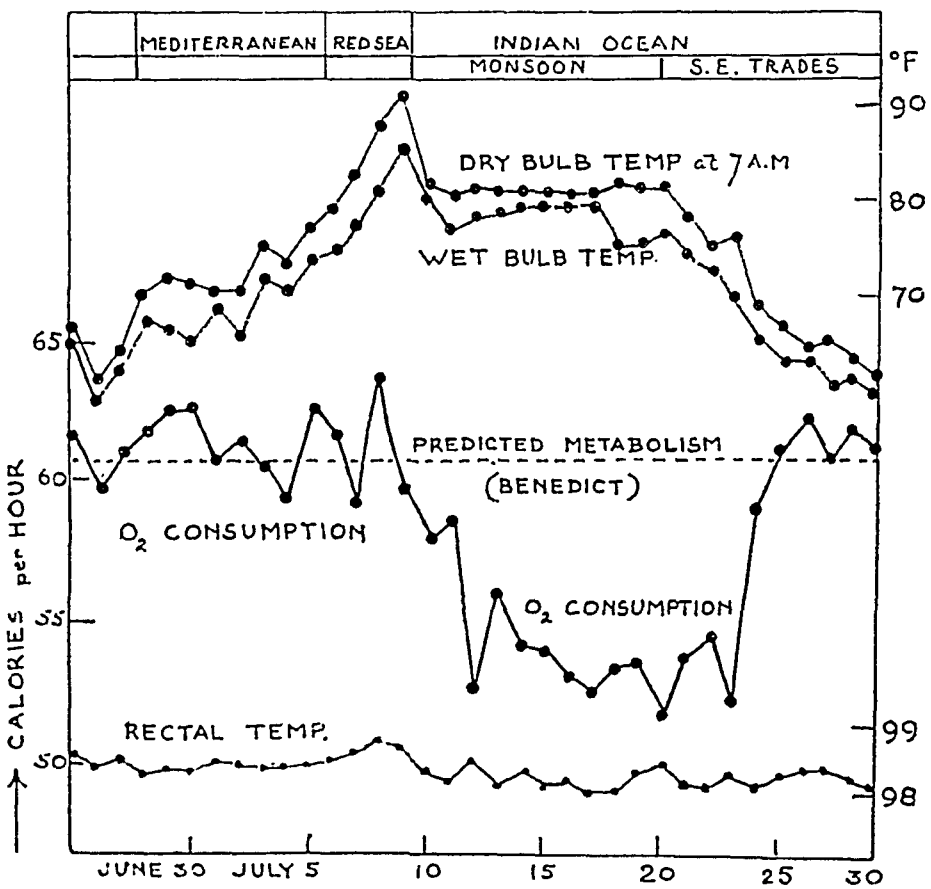

Fig. 6.—Daily observation of basal metabolism of C. J. M. during a voyage from London to Australia, June-July 1923, and daily record of the temperatures of the dry and wet bulb thermometers at 7 A.M. (From Martin, C. J.: Thermal Adjustments of Man and Animals to External Conditions, Lancet 2: 617, 1930.)

frequency of noninfectious arteriosclerotic heart failure onsets, which occurred about two and a half times more frequently in winter than in summer. Just why syphilitic heart failures pursue a course independent of temperature level is not entirely clear. It is probably because of the more rapid course of the disease, with steady progression of the organic lesion.

Explanation of these findings offers great difficulty. A number of possibilities present themselves. It is known that infections, especially of the upper respiratory tract, are most frequent and severe during

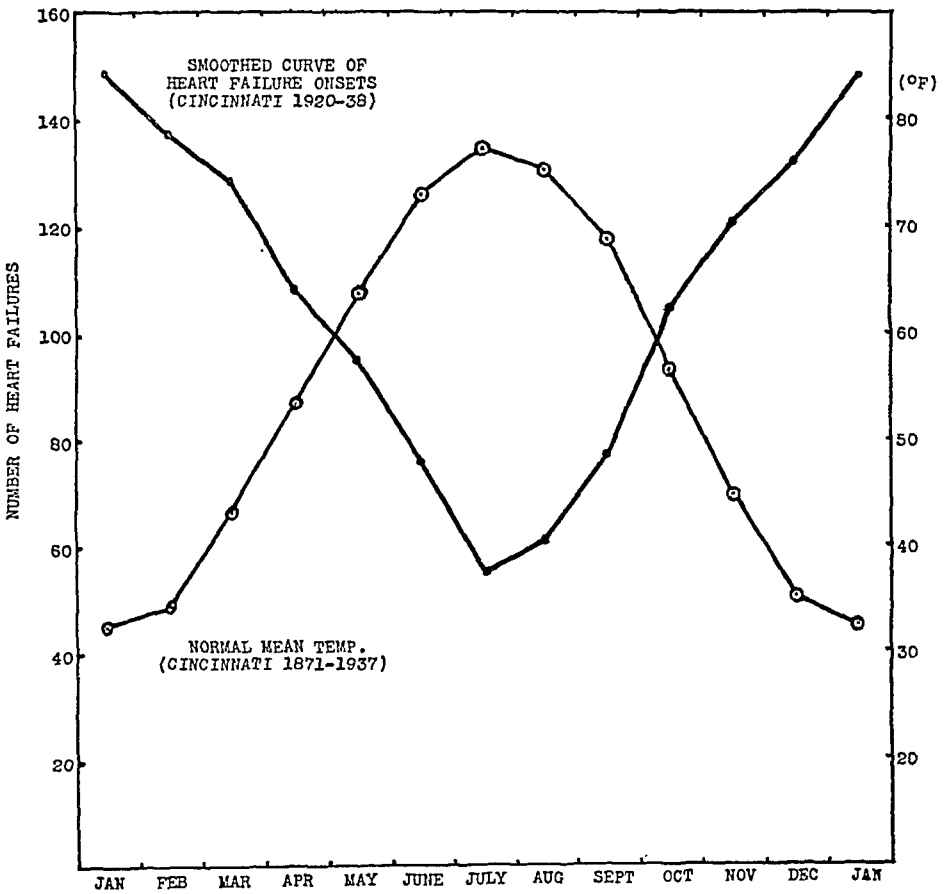

Fig. 7.—Heart failure frequency and mean temperature level.

cold and changeable weather. With these there is a rise in temperature and metabolism, which increases the burden on the heart. When the weather is stormy, fluctuations in temperature may produce a strain by little-known vasomotor reflexes. At least it is known that angina pectoris is likely to be precipitated by walking in cold or windy weather. Certain forms of voluntary activity are also increased in the cold. Such factors increase the burden of the heart and make the life of a cardiac cripple more precarious.

Another factor which may be of fundamental importance is the possible variation of metabolism with change in environmental temperature.

Though a conclusive study of the effect of external environment on metabolism has not been carried out, and though there is no agreement among authorities [Lusk[7]] as to the validity of numerous divergent opinions expressed in the literature, there is an increasing body of evidence on the subject. In Fig. 5 the value obtained on a single individual illustrates a clear inverse relationship between temperature and metabolism [Gessler[7]]. In Fig. 6 are recorded the effects of passage from England to Australia through tropical heat. There are many other reports conveying this same idea for man and animals [Martin[7]]. There is a remarkable similarity between the graphs of Figs. 5 and 7, which show the relation of mean monthly temperature level to oxygen consumption (Fig. 5) and to arteriosclerotic heart failure onsets through the seasons of the year (Fig. 7).

If further evidence is found that external temperature does produce such an effect, it will have an important bearing on the heart failure problem, because it has been shown[8] that the metabolic cost of work performed during activity has a direct relationship to the resting oxygen consumption. The higher the resting metabolic rate, the greater the combustion cost for a given amount of work. The more sluggish individual of the tropics can perform more work on a given amount of combustion than can the more energetic northerner who wastes much of his energy maintaining a higher muscle tone. The northerner can do more work in a unit of time, but he pays a higher price per work unit. As a metabolic machine, he is less efficient.

One of us[9, 10] has discussed the low prevalence of arteriosclerotic and rheumatic heart disease in tropical or subtropical countries as contrasted to their severity in middle temperate regions. The present findings may be taken to support these conclusions. In addition, some metabolic diseases have been found to show a close relationship to climatic and seasonal stress.[11]

SUMMARY

Coronary occlusion attacks are definitely more frequent in winter than in summer in the north temperate regions studied.

In arteriosclerotic and rheumatic patients heart failure is likewise much more frequent in winter cold than in summer warmth; failure onset exhibits a close inverse relationship to mean temperature level in Cincinnati. This group also shows a marked reduction in frequency during warmer and less stormy years, such as came from late 1929 to 1933.

Syphilitic heart failure from aortic insufficiency, however, failed to exhibit any such significant relationship.

Greater frequency of infections and heightened general body metabolism probably act together to increase the winter hazards of existence for cardiac patients, while the calm warmth of summer brings a period of relative safety.

Migration out of northern cold and storms, either temporarily or permanently, is strongly indicated for every patient of limited cardiac reserve whose financial means permit such a course.

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BACTERIAL ENDOCARDITIS SUPERIMPOSED ON SYPHILITIC AORTITIS AND VALVULITIS

A Clinicopathological Study With 5 Case Reports*

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CLINICALLY, it is axiomatic that bacterial endocarditis rarely occurs in an aorta or on an aortic valve previously damaged by syphilis. Pathologic studies have confirmed this. Only five cases in which the existence of such a combination was proved have been reported in the literature up to the present time. The probable pathogenesis has been reviewed by McMillan and Wilbur,[1] Cotton,[2] Briggs,[3] and Bayne-Jones,[4] and will not, therefore, be discussed here.

In a series of 17,000 autopsies at the Los Angeles County General Hospital, 157 cases of vegetative endocarditis were found. Of these there were only 5 cases in which vegetative endocarditis was associated with syphilitic aortitis or valvulitis. Each of these cases presented, in addition, other unusual features. A review of these cases, including clinical and autopsy observations, is herein presented in detail.

Case 1.—Los Angeles County General Hospital, P. F. No. 458-742, Autopsy No. 16964.

E. W., a 61-year-old white sailor, was admitted to the hospital Nov. 11, 1936, with a history of shortness of breath of two years' duration. Otherwise, he had been relatively well until three weeks prior to admission, when he began to have nocturnal dyspnea. One week later he noticed moderate palpitation, and the following week he developed edema of the ankles.

The past history was essentially negative, except for a chancre at the age of 15 years, for which he received no treatment. He denied having had gonorrhea. There had been no serious illnesses and no operations, except a prostatectomy by transurethral resection in 1935.

Physical Examination.—The patient appeared markedly dyspneic and acutely ill. His blood pressure was 175/34; temperature, 97.4° F.; pulse rate, 120; and respiratory rate, 28. The pupils were irregular and reacted very slightly to light, but well in accommodation. There was marked pulsation of the vessels of the neck, with venous engorgement. Examination of the lungs revealed diminished resonance at the bases posteriorly, with many moist râles. His heart was enlarged to the left and downward, and a diastolic murmur was heard at the mitral area. There was a to-and-fro murmur over the aortic area. The pulse was of the Corrigan type. The abdomen was slightly distended, and the liver was palpable three fingerbreadths below the right costal margin. The penis and scrotum were edematous, but otherwise normal. There was marked edema of the lower extremities extending upward

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to the crests of the ilia. Rectal examination revealed a small, hard, nodular prostate. The deep reflexes were absent and position sense was markedly impaired. There was inability to distinguish between dull and sharp.

Laboratory Examination.—The blood Wassermann and Kahn reactions were strongly positive. The hemoglobin was 80 per cent (Sahli); the erythrocyte count, 4,800,000; and the leucocyte count, 8,000, 68 per cent of which were polymorphonuclear leucocytes. The urine was negative except for an occasional granular cast. The orthodiagram showed cardiac enlargement. The aorta was large, but not aneurysmal, and there were calcified plaques in its wall. The electrocardiogram on Nov. 12, 1936, showed left axis deviation and evidence of myocardial and coronary disease. On Nov. 16, 1936, the electrocardiogram was the same except for the occasional occurrence of ventricular extrasystoles. On Nov. 18, 1936, the rhythm had changed to auricular flutter with 2-to-1 block. On Nov. 23, 1936, sinus rhythm was again established. There were changes in the S-T segment in Leads I and III which were suggestive of coronary occlusion, but were not considered diagnostic in view of the complete digitalization.

Progress.—His condition remained poor and although he was digitalized and received theocin and salyrgan, he continued to grow worse. Two days prior to death his temperature became elevated to 100.2° F., where it remained until death, on Dec. 8, 1936.

Autopsy.—The autopsy (No. 16964) was done six and a half hours after death by one of us (W. L. A.).

External examination revealed a well-developed, poorly nourished white man about 60 years of age. The neck vessels were distended, and there was moderate edema of the lower extremities and scrotum.

The skull and central nervous system were grossly normal.

The pericardium appeared to be normal. The heart weighed 750 gm., and the cardiac enlargement was generalized. The apex extended outward to the fifth intercostal space in the anterior axillary line. The epicardial surface was smooth except for a white "soldier" spot on the anterior ventricular wall. The right auricle was moderately distended with clotted blood and the auricular appendage contained several small thrombi. The tricuspid ring was dilated, but the leaflets were normal. The right ventricle was moderately dilated and the wall hypertrophied, measuring from 4 to 8 mm. in thickness. The left auricle was dilated, and the auricular appendage was clear. The mitral ring was moderately dilated, measuring 13 cm. in circumference. Both leaflets were slightly thickened, and there was a ragged perforation, measuring 6 mm. in diameter, of the posterior leaflet. The left ventricular chamber was moderately dilated and the wall hypertrophied, measuring 2 cm. in average thickness. The aortic valve was shown to be incompetent by the water test, and when opened was found to measure 10 cm. in circumference. There were mild thickening, slight calcification, and rolling of the edges of all cusps, with retraction downward and spreading of the commissures, which measured 6-10 mm. in width. The right and posterior cusps showed identical perforations through their walls, measuring 5 mm. in diameter. There were small friable vegetations around the edges of these perforations.

Just proximal to the posterior commissure there was a mycotic aneurysm in the membranous septum measuring 8 mm. in diameter and filled with ante-mortem thrombus. Small friable vegetations surrounded the edges of this sac. Another saccular aneurysm 1 cm. in diameter was found just proximal to the left commissure, and extended 1 cm. into the folds of the membranous septum. This was also filled with thrombus, and friable vegetations were present on the edge of this sac.

Aside from some narrowing of the orifice of the right coronary artery, the vessels appeared normal throughout. The aorta was moderately dilated (9 to 11 cm.)

and showed numerous small atheromatous areas as well as pearly gray plaques and longitudinal "tree-bark" wrinklings of the intima which extended into the abdominal aorta. Approximately 2 cm. distal to the orifice of the superior mesenteric artery there was a thrombus, apparently of embolic origin, plugging the lumen. This plug extended for a distance of 1.5 cm. and did not appear to be attached to the wall of the vessel.

Bilateral pleural effusion (800 to 1000 c.c.) was present. In the right lung near the periphery there were two triangular infarcts with ante-mortem clots demonstrable in the vessels supplying these areas. The lungs were otherwise normal. All loops

Fig. 1.—Case 1, Autopsy No. 16964. Photograph of heart. Extensive aortitis with widening of the commissures of the aortic cusps is evident. Straws have been placed through perforations in the cusps and one through a perforation in the mitral leaflet. Between the two aortic cusps bordering the muscle may be seen a mycotic aneurysm surrounded by small vegetations.

of the small intestine, also the cecum and the first portion of the ascending colon, were distended. The serosa was reddish-purple in color. The serosal surfaces were covered with thin, fibrinous exudate, and a small amount of serosanguineous fluid was found in the peritoneal cavity in the pelvis. The liver was slightly enlarged and presented a typical "nutmeg" appearance on gross section. The gall bladder and biliary ducts were normal. The spleen showed a well-marked chronic passive congestion.

Both kidneys revealed marked passive congestion. The ureters and bladder were normal, except for some longitudinal scarring near the trigone at the base of the bladder. The prostate, which was one and a half times normal size, contained a small adenoma. In the periprostatic vessels there were numerous ante-mortem clots.

Microscopic Examination.—Aorta: The intima showed irregular fibrous thickening which in places was quite marked. There was definite calcification in one or two areas. The media contained many small and some fairly large scars surrounded by moderate numbers of round cells. The adventitia showed fibrous thickening, and the vasa vasorum were thickened by an endarteritis which was quite marked in some places. One fairly large arteriole was obliterated by an organized thrombus. Round cells were rather abundant in the perivascular tissues.

Bacteriology.—Smears and cultures from the abdominal cavity, the aortic valve, and spleen, and fluid from the seminal vesicles and prostate revealed the presence of *Streptococcus viridans.*

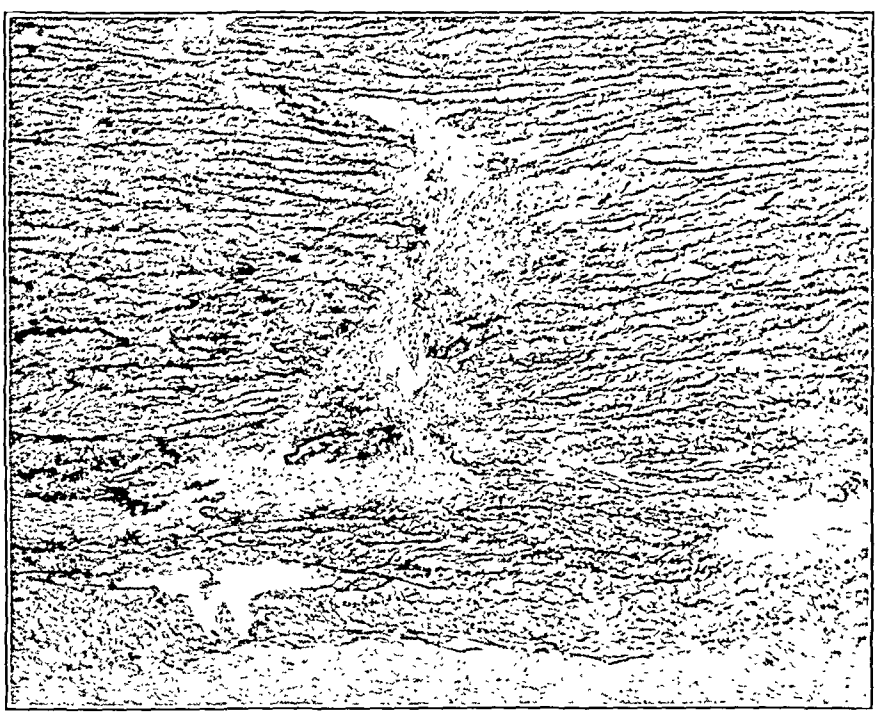

Fig. 2.—Case 1, Autopsy No. 16964. Photomicrograph of aorta showing medial scarring with destruction of elastic fibers (Elastica stain ×95).

Anatomical Diagnosis.—Syphilis of the aorta and aortic valve with insufficiency and cardiac hypertrophy; subacute bacterial endocarditis, aortic and mitral (*Streptococcus viridans*); mycotic, saccular aneurysm, membranous septum and aortic cusps, multiple; mural thrombosis of right auricular appendage; embolism of pulmonary arteries, with multiple infarction of lung; embolism of superior mesenteric artery, with infarction of small intestine, cecum, and ascending colon; acute generalized peritonitis (*Streptococcus viridans*); thrombosis of periprostatic veins; mild hypertrophy of prostate; subacute cystitis; generalized arteriosclerosis; fibrosis of bladder at trigone; operation, transurethral resection, healed.

Discussion.—The diagnosis of syphilis in this case was well established both by the history and the laboratory and pathologic findings. Clinically, the aortitis and aortic insufficiency were quite evident. How-

ever, the presence of bacterial endocarditis was not suspected, and probably justifiably so, inasmuch as there was no fever. Also, the absence of early embolic phenomena was a contributing factor in the failure to make a clinical diagnosis of bacterial endocarditis. The disturbances in the mechanism of the heart beat which occurred two weeks prior to death (change from sinus rhythm to flutter and reversion to normal rhythm upon digitalization) were probably due to the destructive lesion found in the membranous septum at autopsy. Judging from the unusual degree of ulceration with invasion deep into the septum by the bacterial process, one must assume that the lesion was present for a longer time than the clinical manifestations would suggest. One cannot account for the absence of earlier and more abundant embolic phenomena.

CASE 2.—Los Angeles County General Hospital, P. F. No. 474-179, Autopsy No. 14790.

C. W., a 50-year-old male negro, entered the hospital Dec. 29, 1935, in a comatose state. A brief, inadequate history from relatives stated only that he had complained of abdominal cramps about twelve hours before admission. These recurred several hours later and were associated with back pains. Shortly after the recurrence of back pain, the patient fell and lost consciousness.

Physical examination showed that the patient was in a deep stupor. The temperature was 101.8° F. (rectal); the pulse rate, 84; the respiratory rate, 42; and the blood pressure, 52/0. The pupils reacted sluggishly to light, and the eyes were deviated to the right. Moist râles were heard at the bases of the lungs. The heart tones were distant and were obscured by the breath sounds. The abdomen was not remarkable. All the deep reflexes were absent. No pathologic reflexes were obtained. There was flaccid paralysis of the entire left side. The patient expired twelve hours after admission.

Autopsy.—Autopsy No. 14790 was performed eight hours after death by Dr. J. L. Mason, and the following findings were reported. External examination showed a well-developed and well-nourished negro. There were a few petechiae in the conjunctivae. The brain appeared normal externally, but a single coronal section through the mammillary bodies revealed an area of red softening in the thalamus extending out to the cortex. The heart weighed 290 gm. Its chambers, septa, and valves were normal. Immediately distal to the aortic valve in the base of the aorta were seen numerous small, friable vegetations which were easily scraped off. The aorta was not athermatous to any marked degree and did not have the characteristic appearance of syphilitic aortitis, although it showed peculiar longitudinal corrugations of the intima.

The lungs showed only moderate congestion. The peritoneal cavity was dry. The small and large bowel were distended with serosanguineous fluid. Numerous areas of purple discoloration were seen, but no thrombi were found in the superior mesenteric artery or its branches. Recent infarcts were present in both kidneys. The skeletal, endocrine and genital systems were normal.

Microscopic Examination.—Vegetation on Aorta: Microscopic sections of the vegetation revealed an organizing fibrinous mass in which cocci were demonstrated by means of the Gram-Weigert stain.

Aorta: There was marked irregular fibrous thickening of the intima with areas of necrosis in the deeper parts, and patches of heavy cellular infiltration (in the proximity of the aortic vegetation). The media was greatly disrupted by large scars which were heavily infiltrated with round cells. The adventitia was thickened

and showed extremely heavy round-cell infiltration which was not limited to the vessels. Endarteritis was severe in the small arterioles, almost closing a number of them.

Laboratory Findings.—No post-mortem blood culture was taken. The post-mortem blood Wassermann reaction was strongly positive. The post-mortem culture of the vegetations on the aorta showed *Streptococcus viridans.* The culture from the spleen showed no growth.

Anatomical Diagnosis.—Syphilis of aorta; mycotic aortitis at root of aorta; embolism of cerebral arteries, with cerebral softening on right side; bilateral embolism of renal arteries, with multiple infarction of kidneys; embolism of mesenteric arteries, with infarction of small and large bowel.

Discussion.—Because of the fact that the patient was comatose on entry and was in the hospital less than twenty-four hours before death,

Fig. 3.—Case 2, Autopsy No. 14790. Photomicrograph of aorta showing endarteritis of the vasa vasorum, fibrous thickening of adventitia, and heavy round-cell infiltration (hematoxylin and eosin stain ×95).

the history was incomplete. Autopsy disclosed the presence of syphilitic aortitis. That there was a superimposed bacterial aortitis was evident from the septic emboli which were found in the brain, kidneys and intestines, as well as from the fact that the *Streptococcus viridans* grew in the post-mortem culture from the aortic vegetations.

CASE 3.—Los Angeles County General Hospital, P. F. No. 343-434, Autopsy No. 16170.

R. F., a 43-year-old Mexican housewife, entered the hospital April 24, 1936, because of vaginal bleeding, associated with a mucopurulent vaginal discharge of four days' duration, and lower abdominal pain of one month's duration. Prior to this the patient had had no vaginal bleeding for five years. Physical examination at this time revealed a well-developed, middle-aged Mexican woman. The oral tempera-

ture was 100.8° F.; the pulse rate, 120; the respiratory rate, 20; and the blood pressure, 135/70. Positive findings included questionable enlargement of the fundus of the uterus, which appeared fixed and somewhat soft; thickening of both broad ligaments; tenderness in the left lower quadrant; a purpuric eruption of the skin of the legs and feet; pupils which reacted poorly to light, but reacted well in accommodation; and a systolic murmur over the apex of the heart.

While she was in the hospital, her temperature was elevated to 100-101° F. daily. The blood Wassermann reaction was found to be strongly positive. Diagnoses of pelvic inflammatory disease and syphilis were made, and the patient was discharged May 12, 1936. The patient was treated in the Venereal Disease Clinic after discharge. She received 0.1 gram of bismocymol on May 18, June 17, and June 24, 1936. On May 22, 1936, a spinal puncture was done; the cell count, the globulin content, and the pressure were normal, and the Wassermann and Kahn tests were negative. One week following the spinal puncture, she developed headache and vomiting which persisted for two weeks.

She was readmitted to the hospital July 13, 1936. Physical examination revealed that the oral temperature was 100° F.; the pulse rate, 102; the respiratory rate, 22; and the blood pressure, 128/72. The patient was conscious and rational. There was moderate rigidity of the neck. There was a generalized lymphadenopathy. A bismuth line was noted on the gums. There was a petechial eruption over the abdomen. A systolic murmur was noted at the apex.

A spinal puncture was again performed. The initial pressure was 270 mm. of water. The fluid was cloudy; it contained 2000 cells per cubic millimeter, mainly polymorphonuclear leucocytes. No organisms grew in the culture. The spinal fluid sugar was 87 mg. per 100 c.c.

The treatment consisted of repeated spinal punctures. *Streptococcus viridans* was found on one culture. The spinal fluid Wassermann was repeatedly negative. A blood Wassermann on July 15, 1936, was negative. One blood culture showed a large gram-positive rod which was considered a contaminant. The meningeal signs cleared, and the patient appeared remarkably improved. However, she suddenly became cyanotic and dyspneic and died very abruptly on July 21, 1936.

Autopsy No. 16170 was performed by one of us (H. E. M.) eighteen hours after death.

Numerous small petechiae were seen over the trunk and extremities.

The brain showed marked pial congestion with a very small amount of milky, nonpurulent fluid in the sulci over the vertex. Numerous coronal sections of the brain revealed no abnormalities.

Petechiae were seen in the visceral pericardium. There were firm, fibrous, pericardial adhesions between the aorta and pulmonary artery at the base of the heart. Section was made through this area and thick, yellow-green pus was found just beneath the pericardium in the small triangular space between the origin of the aorta and the pulmonary artery. This abscess communicated directly with a vegetation on the aorta, which had perforated the wall. The heart weighed 530 gm. The chambers on the right side of the heart appeared moderately dilated. The left ventricle also showed dilatation. Its wall averaged 1 cm. in thickness. The tricuspid, pulmonic, and mitral valves were normal. Several small, pale yellow plaques were seen in the free margins of the cusps of the aortic valve. The commissures showed slight widening. The base and attachment of the aortic valve appeared to be calcified. About 1 cm. above the aortic ring there were several ulcerated plaques in the intima of the aorta. On one of these there was a grayish yellow vegetation which measured approximately 5 mm. in diameter. This vegetation had eroded through the wall of the aorta and communicated directly with the small abscess cavity previously described. The aorta showed some longitudinal wrinkling of the

intima and occasional white, elevated plaques in the thoracic portion. Elsewhere, the intima was smooth. The coronary arteries and myocardium appeared normal.

The lungs showed marked edema and bilateral, healed, apical tuberculosis. The spleen weighed 275 gm. and showed moderate softening. A fibromyoma of the uterus was found, as well as a submucous, endometrial polyp. Both tubes and ovaries were prolapsed into the cul-de-sac, where they were adherent to each other and to the adjacent structures. The tubes were moderately dilated. The ovaries appeared normal on cross section. The kidneys showed a peculiar mottled reddish yellow appearance.

Microscopic Examination.—In the aorta in the region of the vegetation there were deposits of fibrin in which were entangled large collections of disintegrated polymorphonuclear cells, red blood cells, and occasional fibroblasts, replacing large areas of the intima, which appeared ulcerated. The media showed areas of necrosis and

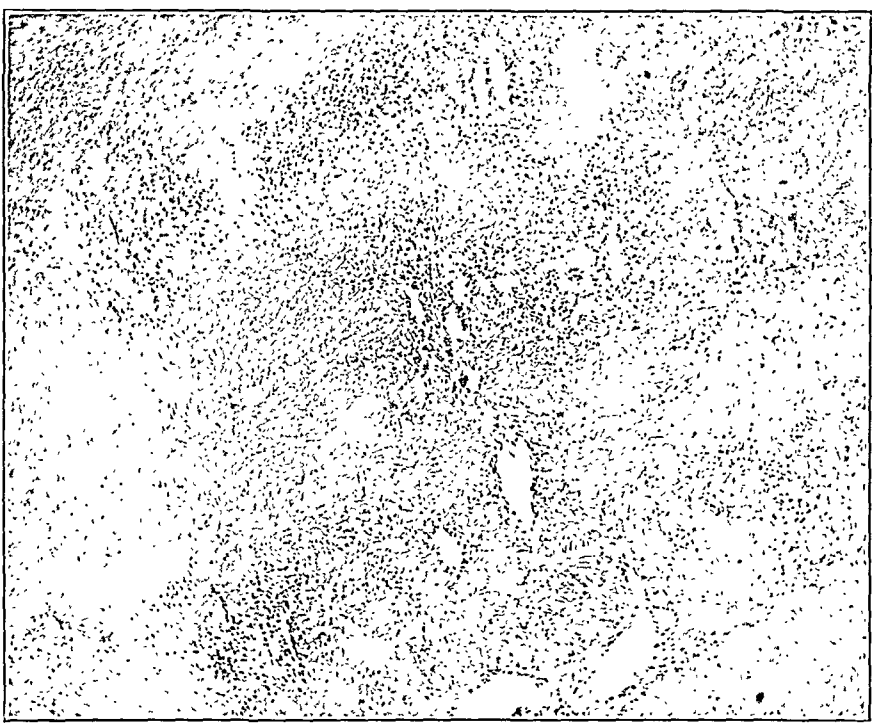

Fig. 4.—Case 3, Autopsy No. 16170. Photomicrograph of aorta. Scarring is evident about the vasa vasorum of the media with more or less round-cell infiltration (hematoxylin and eosin ×95).

ulceration similar to those in the intima and continuous with them. In several areas in the media there were large collections of round cells, mainly perivascular in distribution.

Elsewhere in the aorta the intima was only moderately thickened by loosely arranged cellular connective tissue. The media contained a moderate number of small scars surrounded by quite heavy round-cell infiltration. Other areas showed marked destruction of the media by large, almost confluent scars. A good many polymorphonuclear leucocytes were found in these areas. Endarteritis of the adventitial arterioles was marked, with eccentric thickening of the walls. Dense accumulations of round cells were found about the vessels and well into the adjacent adipose tissue. Fibroblasts were present in several areas.

Laboratory Findings.—A hemolytic streptococcus was recovered from the blood post mortem.

Anatomical Diagnosis.—Syphilis of aorta and aortic valve, with cardiac hypertrophy; septic thrombosis of aorta, with perforation and abscess formation involving base of heart; septicemia (*Streptococcus hemolyticus*); acute septic splenitis; purulent meningitis, healed; fibromyomas of uterus; polyp of uterus; subacute cystitis; acute, bilateral pyelitis; bilateral apical, healed, pulmonary tuberculosis; chronic bilateral oophoritis and salpingitis.

Discussion.—The diagnosis of syphilis was established clinically in this case, although no history was obtained as to the time of infection. The septicemia and the vegetative aortitis were not discovered until autopsy, although the patient presented purpuric phenomena and had fever and irregular menstrual bleeding several months before death. It is of interest that the embolic meningitis had practically cleared up before death. At autopsy there was no evidence of syphilis of the central nervous system. The principal syphilitic lesion of the cardiovascular system was in the aorta, although early changes were present in the aortic valve. It is of interest that the vegetation in the aorta had perforated the wall of the vessel in the one location where a perforation could be readily walled off, i.e., near the base of the heart. Although one spinal fluid culture, ante mortem, was reported as containing *Streptococcus viridans,* all of the post-mortem cultures showed *Streptococcus hemolyticus.*

CASE 4.—Los Angeles County General Hospital, P. F. No. 283-667, Autopsy No. 16645.

L. T. F., a 28-year-old white male chemist, came to the hospital April 5, 1935, because of abdominal pain and vomiting. One year before an appendectomy had been done. Physical examination gave essentially negative results, except that the aortic second sound was replaced by a to-and-fro murmur. The blood Wassermann and Kahn reactions were strongly positive. The abdominal pain disappeared, and the patient was referred to the Venereal Disease Clinic for treatment.

He was readmitted in May, 1936. Additional history at this time revealed that he had suffered from dyspnea and precordial pain on exertion since 1934. There was no history of a chancre. He had had acute urethritis in 1927, which had been followed by polyarthritis for six months. Examination revealed a to-and-fro murmur in the aortic area and a diastolic murmur and thrill at the apex. Capillary pulsations and Duroziez' sign were present. The blood pressure was 170/30.

The final admission was on Oct. 3, 1936. The patient returned to the hospital because of increased weakness, loss of weight, and severe night sweats. The cardiac findings were the same as in May, 1936. There was daily elevation of the temperature to 100° F., and the pulse rate was 100 to 120 per minute. Petechiae were seen in the conjunctivae. The spleen was easily palpable at the costal border.

Laboratory Examination.—The hemoglobin was 70 per cent (Sahli); the erythrocyte count, 3,900,000; and the leucocyte count, 8,000. The urine contained no albumin, casts or cells. An orthodiagram showed marked cardiac enlargement, predominantly left ventricular. The electrocardiogram revealed signs of myocardial impairment and left axis deviation. *Streptococcus viridans* was found in three separate blood cultures.

Autopsy No. 16645 was performed by one of us (H. E. M.) three and one-half hours after death.

Fig. 5.

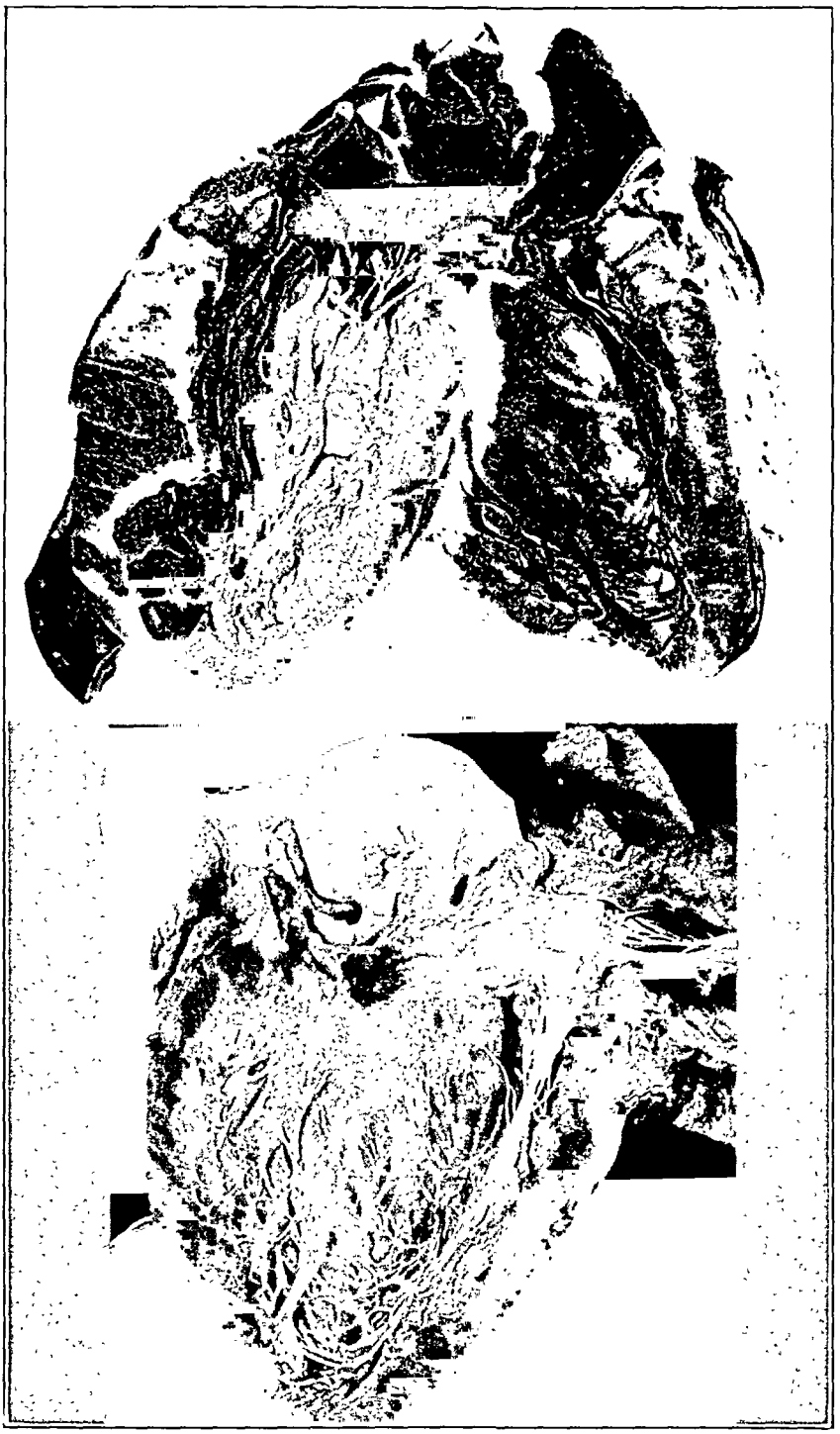

Fig. 6.

Fig. 5.—Case 4, Autopsy No. 16645. Photograph of the heart. The mitral valve shows fibrous thickening and fusion of the leaflets, thickening and shortening of the chordae tendineae, evidently an old rheumatic lesion. A bacterial vegetation covers the posterior leaflet. The wall of the auricle is definitely thickened.

Fig. 6.—Case 4, Autopsy No. 16645. Photograph of the heart. This shows widening of the commissures of the aortic valve with shortening and rolling of the cusps. A peculiar, depressed, scarlike plaque is present immediately above the middle commissure. A block for section has been removed from a similar lesion to the left of the right coronary ostium. Elsewhere the base of the aorta is very smooth.

There was marked thickening of the pia-arachnoid, with areas of fibrosis over the vertex of the brain. Small petechiae were scattered throughout the white substance of the brain.

There were many fibrous plaques in the visceral pericardium over the anterior surface of the heart, as well as diffuse thickening of the parietal pericardium. The heart weighed 600 gm.; the cardiac hypertrophy was practically limited to the left ventricle and left auricle. The right auricle was moderately dilated. The right ventricle appeared approximately normal in size. The wall of the left auricle was between two and three times thicker than normal and showed areas of scarring in its endocardium. Both auricular appendages appeared normal. The tricuspid valve showed slight thickening of the leaflets, but was not otherwise remarkable. It measured 11.5 cm. in circumference. The pulmonic valve was normal and measured 8 cm. in circumference. The mitral valve showed fibrous thickening of the leaflets, with one area of calcification along the line of attachment at the base of the valve.

Fig. 7.—Case 4, Autopsy No. 16645.—Photomicrograph taken through the plaque in the base of the aorta (see Fig. 6). There are marked fibrous thickening and heavy round-cell infiltration of the adventitia. The outer part of the media is also involved.

There were some thickening and shortening of the chordae tendineae. There was a large, yellow, granular, heaped-up vegetation on the mitral valve, approximately 2 cm. in diameter. In addition, there were numerous pinpoint vegetations along the line of closure. The mitral ring measured 9.5 cm. in circumference. The aortic valve was markedly distorted and displaced downward. Its circumference was 7.2 cm. The commissures appeared widened and there was rolling of the free margins of the cusps. There were ulceration and scarring of the cusps by large, granular vegetations similar to those on the mitral valve. Just above the aortic ring in the aorta were two pearly white plaques. These plaques extended down to the commissures and appeared to widen them. The pulmonary artery and the coronary arteries were essentially normal. Repeated broad sections of the myocardium revealed a dark red heart muscle in which were scattered many small and large areas of fibrosis.

Recent infarcts were seen in the spleen and kidneys. Bronchopneumonia was present. No other positive findings were recorded.

Microscopic Examination.—Heart: Several sections revealed large areas of dense scarring. Elsewhere many smaller scars were present, some in the form of narrow bands of fibrous tissue. The muscle fibers were hypertrophied and irregularly arranged. Occasional areas of recent necrosis were seen. Many large mononuclear cells of elongated form, together with occasional lymphocytes and polymorphonuclear leucocytes, diffusely infiltrated the interstitial tissue. Several typical Aschoff bodies were seen in sections of the interventricular septum.

Aorta, Through Plaque: The intima was markedly thickened by dense fibrous tissue which contained some pale atheromatous areas. The media in this region was much thinned and scarred. Heavy deposits of round cells were found about the scars and extending into the adjacent portions of the adventitia. The latter was markedly thickened and densely fibrous in this area. Small perivascular collections of round cells were scattered throughout. A moderate amount of endarteritis was present.

Laboratory Findings.—*Streptococcus viridans* was recovered from the vegetation on the heart valve.

Anatomical Diagnosis.—Syphilis of aorta, focal; syphilis of aortic valve with insufficiency and cardiac hypertrophy; chronic rheumatic endocarditis, mitral valve; subacute bacterial endocarditis, mitral and aortic valves (*Streptococcus viridans*); embolism of splenic artery, with infarction of spleen; embolism of renal artery, with infarction of kidneys, and terminal bronchopneumonia.

Discussion.—On the last two admissions it was thought that the heart disease was rheumatic in origin, with involvement of the aortic and mitral valves and superimposed bacterial endocarditis. Pathologically, the heart valves were thought to be the seat of a double lesion, viz., syphilitic valvulitis of the aortic valve, and rheumatic endocarditis of the mitral valve.

Syphilitic involvement of the aorta by two focal lesions with the remainder of the intima normal in appearance is extremely rare. It may be questioned whether such lesions are of syphilitic origin. The changes in the aortic valve, however, in no way resembled rheumatic endocarditis. The commissures in the vicinity of the aortic plaques were definitely widened, and the free edges of the cusps were rolled and somewhat shortened. The microscopic picture was that of syphilis, as described above. The infiltrating cells were of the lymphocytic and plasma cell varieties rather than of the large mononuclear type seen in rheumatic lesions. In addition, the positive serologic reactions strengthen the evidence that the lesions were syphilitic.

CASE 5.—Los Angeles County General Hospital, P. F. No. 457-597, Autopsy No. 14326.

T. P. J., a negro, aged 42 years, a bootblack, was additted to the hospital Sept. 25, 1935. He was in excellent health until Sept. 9, 1935, when, upon returning from work, he had a chill followed by a fever of 103° F. Following this he had a severe headache, became extremely weak, and upon trying to get out of bed fainted and fell to the floor. He remained in bed at home until the morning of admission, when he again had a fainting spell. Aside from slight palpitation and dyspnea on exertion, he had been without symptoms until the onset of the present illness.

The past history was irrelevant except for the fact that he had had a chancre at the age of 16, following which he received sixteen "intravenous injections."

Physical examination showed that the patient was fairly well developed. The temperature was 101.3° F.; the pulse rate, 80; the respiratory rate, 34; and the blood pressure, 134/0. The right pupil was irregular, but both pupils reacted well to light and in accommodation. There were "explosive" carotid pulsations in the neck. The fingers showed definite clubbing, and the pulse was of the Corrigan type. The lungs were normal except for crackling râles at the left base. There was a heaving precordium with the point of maximum intensity centered in the fifth interspace just to the left of the nipple. There was a palpable diastolic thrill at the apex. There was also a soft, low-pitched systolic murmur in the aortic area. There was a loud, blowing, to-and-fro murmur at the apex which was transmitted upward toward the base. The rhythm was normal. The abdomen was essentially negative. There was no dependent edema. The reflexes were normal.

Laboratory Examination.—The blood Wassermann and Kahn reactions were strongly positive. The hemoglobin was 65 per cent (Sahli); the erythrocyte count, 2,750,000; and the leucocyte count, 26,000; the differential leucocyte count showed that 88 per cent were polymorphonuclears, 8 per cent lymphocytes, 3 per cent monocytes, and 1 per cent basophils. The urine was normal. Blood cultures made Oct. 4 and 8, 1935, remained sterile.

A roentgenogram of the chest, made Oct. 1, 1935, led to a diagnosis of aortic heart disease. Agglutination tests for typhoid and undulant fever, done Oct. 12, 1935, were negative.

Course.—The patient continued to run a fever of 101 to 103° F., and on Oct. 4, 1935, a friction rub was heard at the apex of the heart. He grew progressively worse, and expired October 12.

Autopsy No. 14326 was done by Dr. J. P. FitzGibbon twelve hours after death. The body was that of a well-developed, middle-aged negro male, showing no gross abnormalities.

The pericardial sac was tremendously enlarged, and when it was opened it seemed to enclose snugly the large heart; the visceral pericardium was tremendously roughened by a heavy, shaggy, fibrinous exudate, which was firm and more or less organized. This process was less marked on the parietal pericardium. The heart weighed 750 gm. The right auricle and ventricle were approximately of normal size. The left auricle was slightly enlarged and the left ventricle was greatly enlarged and thickened, the wall averaging 1.9 cm. in thickness. The endocardial surface of the left ventricle showed marked tigering. The valves were normal, except for the aortic valve, whose edges were rolled and whose mitral cusp was the seat of an acute process which had progressed to the formation of a mycotic aneurysm with rupture at one point. One centimeter below the aortic orifice, in the region of the septum, there was a square patch about 1 cm. across which was slightly raised, firm, and, when cut, appeared as a yellow-gray, necrotic plaque. The aorta was the seat of a number of "tree-bark" wrinklings and, in addition, showed many areas of arteriosclerotic involvement. Each pleural cavity contained 500 c.c. of thin, straw-colored fluid.

Unfortunately no microscopic examination of the aorta was made in this case, and there is no material available for study.

Laboratory Findings.—*Streptococcus viridans* and *E. coli* were recovered from the vegetation. A culture from the pericardium became contaminated.

Anatomical Diagnosis.—Syphilis of aorta and aortic valve with insufficiency and cardiac hypertrophy; acute bacterial endocarditis; subacute fibrinous pericarditis; and splenic tumor, septic.

Discussion.—This is a fairly typical case of combined bacterial endocarditis and syphilitic valvulitis, both from the clinical and gross patho-

logic standpoints. The febrile course was septic from the onset of the final illness. It is unfortunate that more attempts were not made to obtain a positive blood culture prior to death.

SUMMARY

Five cases of proved syphilitic endocarditis or aortitis, with superimposed bacterial vegetations, have been presented. In none of the cases were both diagnoses made clinically. In all five cases the blood Wassermann and Kahn reactions were positive. In four cases blood cultures were positive, and in the fifth case *Streptococcus viridans* was grown from the vegetation on the heart valve.

Streptococcus viridans was recovered in four of the cases and *Streptococcus hemolyticus* in the remaining case. In three of the cases embolic phenomena were prominent, and in two the mesenteric vessels were involved. In one case there were multiple saccular mycotic aneurysms of the membranous septum and aortic cusps. In another case a fairly characteristic syphilitic aortic valvulitis and aortitis were associated with a typical rheumatic involvement of the mitral valve.

The diagnosis of syphilitic aortitis and valvulitis does not exclude the possibility of superimposed bacterial involvement, as shown by the above cases, although the lesion undoubtedly is rare. This diagnosis should be considered clinically whenever there is a combination of sepsis of undetermined origin, a positive Wassermann reaction, and evidence of aortic insufficiency or aortitis, without evidence of previous rheumatic infection.

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COMPLETE TRANSPOSITION OF THE GREAT VESSELS

Clinical and Pathologic Features*

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COMPLETE transposition of the great vessels is such a striking malformation of the heart that it has attracted the attention of a number of investigators. During recent years most of the studies[1-5] have been directed toward the origin of this condition. Various theories based upon embryologic, morphologic, and phylogenetic studies have been advanced. Recently Lev and Saphir[6] reviewed these theories and reported the autopsy findings in 6 cases of complete transposition. There have also been a number of isolated case reports,[7-12] but no progress has been made in regard to the clinical recognition of this condition. In 1930 Kato[13] reviewed 92 cases which had been reported in the literature and added 5 more. He emphasized the wide variety of malformations which occur in association with transposition of the great vessels. His analyses showed that there were no characteristic murmurs or thrills associated with this malformation, and he expressed the opinion that the condition was extremely difficult, if not impossible, to recognize during life. Castellanos and his coworkers[14] have recently made an extensive report concerning the recognition of congenital malformations of the heart by visualizing the chambers of the heart with a radiopaque substance, thorotrast. They claimed that transposition of the great vessels could be recognized by this method because the solution which was injected into the jugular vein passed directly from the right side of the heart into the descending aorta. The method requires special radiologic technique and also involves the risk of possible untoward reactions. Furthermore, the method does not permit differentiation of complete transposition of the great vessels from other malformations in which the blood from the pulmonary circulation is pumped directly into the aorta. Recently, Ingham and Willius[15] have reported five cases; they concluded that there were no characteristic physical signs or symptoms. During the last few years we have had the opportunity to make clinical studies on four cases. The fluoroscopic findings in these cases were sufficiently characteristic to enable the diagnosis to be made during life.

The fundamental feature in cases of complete transposition of the great vessels is the abnormal torsion of the aortic septum, whereby the aorta arises from the right ventricle and the pulmonary artery

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from the left ventricle. Thus the blood is pumped from the right ventricle through the aorta to the systemic circulation and returns via the superior and inferior venae cavae to the right auricle; the blood from the left ventricle is pumped through the pulmonary artery to the lungs and returns by way of the pulmonary veins to the left auricle. Obviously, in order that this malformation may be compatible with life, even for a short time, there must be an additional malformation which permits some crossing of the systemic and pulmonic circulations, i.e., either a patent ductus arteriosus, a patent foramen ovale, an interventricular septal defect, or some combination of these.

It is the large number of variations in the associated anomalies which renders the condition difficult to diagnose during life. These different concomitant malformations produce various changes. Although the quality and intensity of the murmurs and thrills vary according to the nature of the concomitant malformation, they depend primarily upon the relative pressure in the systemic and pulmonic circulations. These several factors permit such wide diversity of physical findings that the murmurs and thrills are of no diagnostic aid. Furthermore, the different combinations of anomalies cause a variety of changes in the size and shape of the heart. This makes the exact diagnosis of the malformation difficult. The problem resolves itself into (1) the recognition of the transposition and (2) an analysis of the concomitant malformations. The purpose of this report is to present the features by which the existence of complete transposition of the great vessels can be recognized during life.

The diagnosis is based primarily upon the changes in the shadow cast by the great vessels, combined with persistent cyanosis. Inasmuch as the right ventricle pumps the unoxygenated blood through the systemic circulation, sooner or later the patient always shows *persistent cyanosis*. Both the time at which the cyanosis becomes apparent and its intensity vary with the concomitant malformation. Although we have seen one infant in whom no cyanosis was visible in the neonatal period, as yet we have not recognized the condition before cyanosis appeared.

The altered position of the great vessels relative to the ventricles causes such a characteristic change in the cardiac silhouette that the condition can be recognized by fluoroscopic examination. The most significant feature is the alteration of the shadow cast by the great vessels. When the aorta arises from the right ventricle and the pulmonary artery from the left ventricle, the aorta lies anteriorly and further to the left than it does in the normal heart, and the pulmonary artery lies posteriorly and further to the right (Fig. 1). Because of this counterclockwise rotation the pulmonary artery comes to lie behind the aorta and the shadow cast by the great vessels is narrow. Upon rotating the infant into the left anterior oblique position, the

pulmonary artery, which in the anteroposterior view was behind the aorta, comes to lie parallel to the aorta and thereby causes the shadow cast by these vessels to increase in width (Fig. 2). By placing one finger behind the other and then rotating the hand 45°, the change in the width of the shadow can be clearly demonstrated. Because of the difficulties in obtaining satisfactory roentgenograms in infancy,* especially in the oblique position, this phenomenon may be difficult to demonstrate. These changes are, however, readily visualized beneath the fluoroscope. They are pathognomonic of the condition.

The shape of the heart is also suggestive. In the anteroposterior view, in addition to the narrow aortic shadow, the heart is seen to be

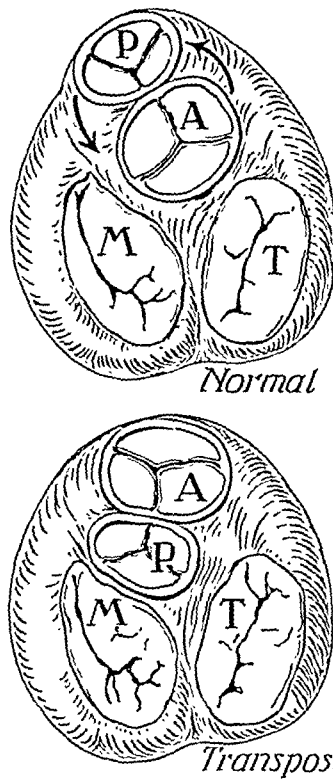

Fig. 1.—The upper diagram shows the base of the heart with auricles removed and the direction of the rotation of the great vessels. (From W. Spalteholtz—*Handatlas der Anatomie.*)

The lower drawing shows the position of the pulmonary artery and aorta in cases of transposition of the great vessels.

enlarged both to the right and the left (Fig. 3). Not only is the heart enlarged, but, inasmuch as the right ventricle pumps the blood through the systemic circulation, there is always specific enlargement of that chamber. This is best recognized under the fluoroscope in the left anterior oblique position; in this view the right ventricle is seen to project forward anterior to the aorta.

*We have had great difficulty in obtaining satisfactory roentgenograms in cases of transposition of the great vessels. Characteristic teleoroentgenograms are shown by Kato,[13] Feldman and Chalmers,[9] and in Abbott's *Atlas of Congenital Heart Disease*[16] (Dr. Nicolson's case, page 54).

The absence of the shadow cast by the pulmonary conus of the right ventricle offers additional evidence that the pulmonary artery occupies an abnormal position. The absence of the pulmonary conus of the right ventricle is due to the fact that the aorta seldom lies as far to the right as does the normal pulmonary artery. Thus, in the antero-posterior view it is usual to find that the shadow ordinarily cast by the pulmonary conus of the right ventricle is absent; this causes a

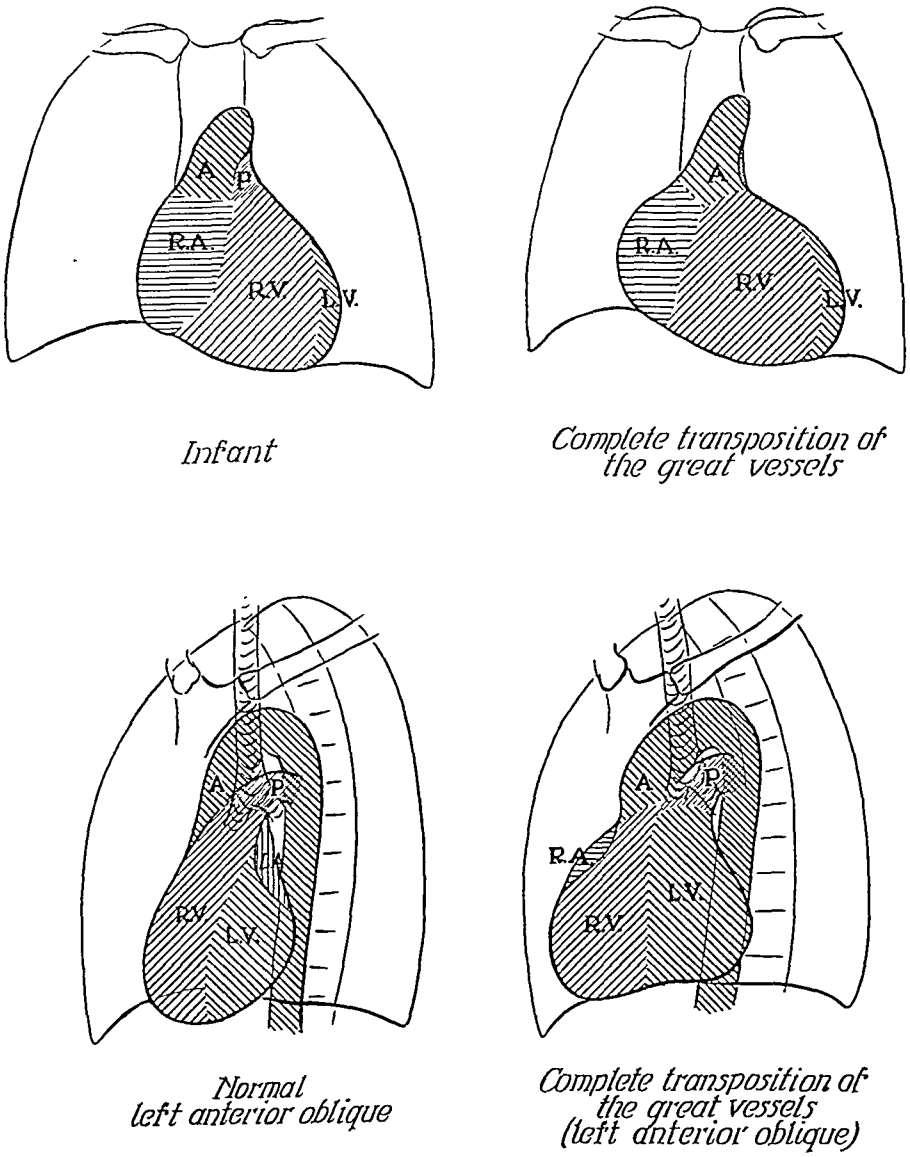

Fig. 2.—The upper diagrams illustrate the anteroposterior view of the heart of the normal infant and when transposition of the great vessels is present.

Note: The great vessels appear narrower in the transposed heart than in the normal heart.

The lower diagrams illustrate the changes which occur in the left anterior oblique position.

Note: In this view the great vessels appear wider than in the normal heart; thus, upon rotation there is a greater change in the width of the great vessels in cases of transposition than occurs in the normal heart. In this position the right auricle may or may not be visible.

slight concavity, rather than a convexity, of the upper border of the cardiac silhouette to the left of the sternum. This abnormality may be so marked as to resemble the contour seen in cases of pulmonary atresia and nonfunctioning right ventricle.[17] Nevertheless, when the infant is rotated into the left anterior oblique position, the two conditions are easily differentiated. In cases in which the right ventricle does not function it is not enlarged, whereas in cases of transposition of the great vessels, the right ventricle is always enlarged.

The electrocardiogram may be of aid in the recognition of right ventricular enlargement. A difficulty arises because in some cases the left ventricle is also enlarged and the enlargement of the right side

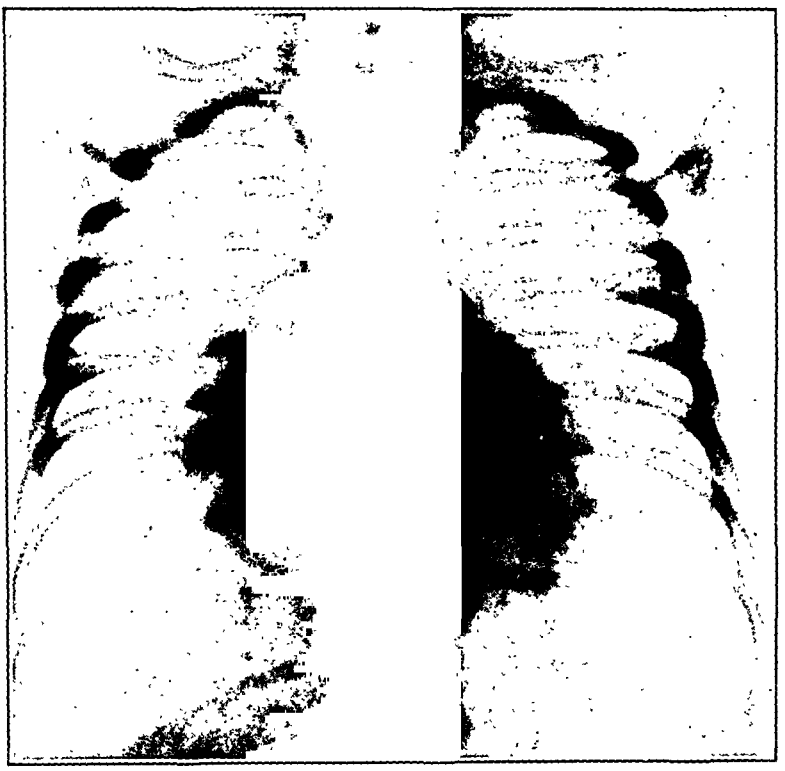

Fig. 3.—Teleoroentgenogram of the chest of an infant with complete transposition of the great vessels combined with a patent foramen ovale, patent ductus arteriosus, and a defect in the interventricular septum.

of the heart may not be sufficiently greater than the left to give right axis deviation. Therefore, the visual evidence of right ventricular enlargement is more reliable than that derived from the electrocardiogram.

As previously stated, this malformation is not compatible with life, even for a short time, unless it is associated with some additional malformation which will permit some admixture of blood between the two circulations. The various combinations of anomalies manifest themselves by slightly different features which are of aid in diagnosis, but the analysis of these manifestations is beyond the scope of the present paper, and will be reported in detail at a later date.

SUMMARY

We have had the opportunity to study four cases of complete transposition of the great vessels clinically and post mortem. In one case there was, in addition, a patent foramen ovale, a patent interventricular septum, and a patent ductus arteriosus; in the second, a patent interventricular septum; in the third, a patent foramen ovale and a patent ductus arteriosus; and in the fourth, a patent foramen ovale, a patent ductus arteriosus, and complete interruption of the isthmus of the aorta. Each had its own individual variations, but all showed the characteristic features of complete transposition of the great vessels, namely, (1) persistent cyanosis; (2) cardiac enlargement, especially of the right ventricle; (3) a narrow aortic shadow in the anteroposterior roentgenogram; and (4) an increase in the width of the roentgenographic shadow cast by the great vessels when the patient is placed in the left anterior oblique position.

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SOME NOTES ON THE ANATOMY OF THE ELEPHANT'S HEART*

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THE rare opportunity to dissect the hearts of two captive elephants is the occasion for the presentation herewith of a few notes concerning our findings.

Its immense size is the feature that has especially aroused the interest of mankind in the elephant. As early as the time of the elder Pliny there were current many stories and speculations about the elephant. Galen[1] described the four chambers which he found in an elephant's heart which was about to be served for luncheon at the emperor's table. Since that day numerous scientific observations have been recorded. These studies have contributed to our store of information in comparative anatomy, furthering our interest in, and our knowledge of, the animal kingdom. Complete and detailed anatomic studies, however, have not often been possible on account of the degenerative changes that usually occur in the tissues in the interval between the death of the animal and the performance of the autopsy. The most recent reports concerning the elephant are those of Hill[2] (1936) and Benedict[3] (1936). The former studied the heart of the wild elephant with especial reference to the coronary vessels. Benedict, of the Carnegie Institution, published a comprehensive review of the literature dealing with the elephant and the results of intensive physiologic studies made on the animal.

In a study of the pulse rate of vertebrate animals, Buchanan[4] shows in general that "the more active animals have relatively the largest hearts and correspondingly the slowest pulses." She finds that the percentage of heart weight in relation to the body weight in the hen is 0.42 per cent, in the pigeon 1.5 per cent, in the deer 1.15 per cent, and in man 0.59 per cent. Pütter,[5] in 1918, stated that the heart weight of the elephant is 0.44 per cent and that of the whale 0.508 per cent of the body weights, respectively. We were impressed by the data gathered from the literature as related to our own observations, which are recorded in Table I. Male elephants, while relatively fewer in number, both wild and in captivity, are usually larger than the females, and those from

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Africa are larger than those from India. It will be seen from Table I that all of the males are of unusually large size. Furthermore it appears that the greater the body weight the less the proportionate size of the heart. The ratio of 1.0 per cent as given by Gilchrist[6] has been thought explainable by the fact that the heart described by him was probably weighed with the chambers filled with blood.

TABLE I

COMPARATIVE WEIGHTS OF ELEPHANTS AND THE RATIO OF HEART TO BODY WEIGHT

OBSERVER	ANIMAL	SEX	BODY WEIGHT	WEIGHT OF HEART	PERCENTAGE OF HEART WEIGHT TO BODY WEIGHT
Fox[7] (1908)	Bolivar	Male	5440 Kg.	19.1 Kg.	0.35
Noback[8] (1931)	Kartoum	Male	4710 Kg.	22.7 Kg.	0.48
White and Burwell (1921)*	Mollie	Female	3710 Kg.	19.3 Kg.	0.52
King (1935)*	Tusko	Male	6491 Kg.	21.9 Kg.	0.34
Gilchrist[6] (1851)			1975 Kg.	19.1 Kg.	1.00

*These are the authors of the present report, publishing for the first time herewith the data on Mollie and Tusko. The years refer to the dates of the dissection of these two hearts.

For detailed studies in comparative anatomy of the heart, the reader is referred to Pütter's[5] interesting and comprehensive work, and to the description of the whale's heart by White and Kerr.[9]

Of recurring interest is Galen's report[1] that he found a "bone in the heart" of the elephant. Retzer,[10] in a review of the literature on the subject, found variance in reports as to the existence of an os cordis. He did not find one in the heart of a young elephant which he dissected. It was his opinion that bone formation, when it did occur, was at the site of the trigone fibrosa. We have not found a histologic description of the os cordis in the elephant which would distinguish between true osseous tissue and simple calcium deposit. An os cordis was not found in either of our specimens, nor was there a significant degree of fibrosis or any calcification in the heart or aorta; this is in distinct contrast to the regular finding of a bone in the ox heart, and its at least occasional finding in the hearts of the sheep and the deer.

CASE REPORTS

CASE 1.—Mollie, an adult female Indian elephant, died in the Franklin Park Zoo, Boston, Mass., at 8 A.M., April 22, 1921. Death was attributed to exhaustion after a twenty-four-hour struggle to arise from the left side "cast." The autopsy was performed the following day. The main portion of the carcass was cut up and disposed of by a fertilizer manufacturer. The skeleton was preserved for mounting at the Agassiz Museum. The heart (Fig. 1) was preserved in formalin and later studied by two of us (P. D. White and C. S. Burwell). The following notes were made at the time.

TABLE II

MEASUREMENTS OF HEART (MOLLIE)

Total weight (chambers empty of blood)	19.3 Kg. (42½ lb.)
Length	24.0 cm.
Breadth	38.0 cm.
Circumference	98.0 cm.
Mitral valve diameter	13.5 cm.
Aortic valve diameter	11.0 cm.
Left ventricle	
Thickness of wall (midway)	5.0 cm.
Thickness of wall (apex)	2.0 cm.
Aorta	
Outside diameter	12.5 cm.
Internal diameter	7.5 cm.
Thickness of wall	2.5 cm.
Diameter of coronary arteries (internal)	1.0 cm.

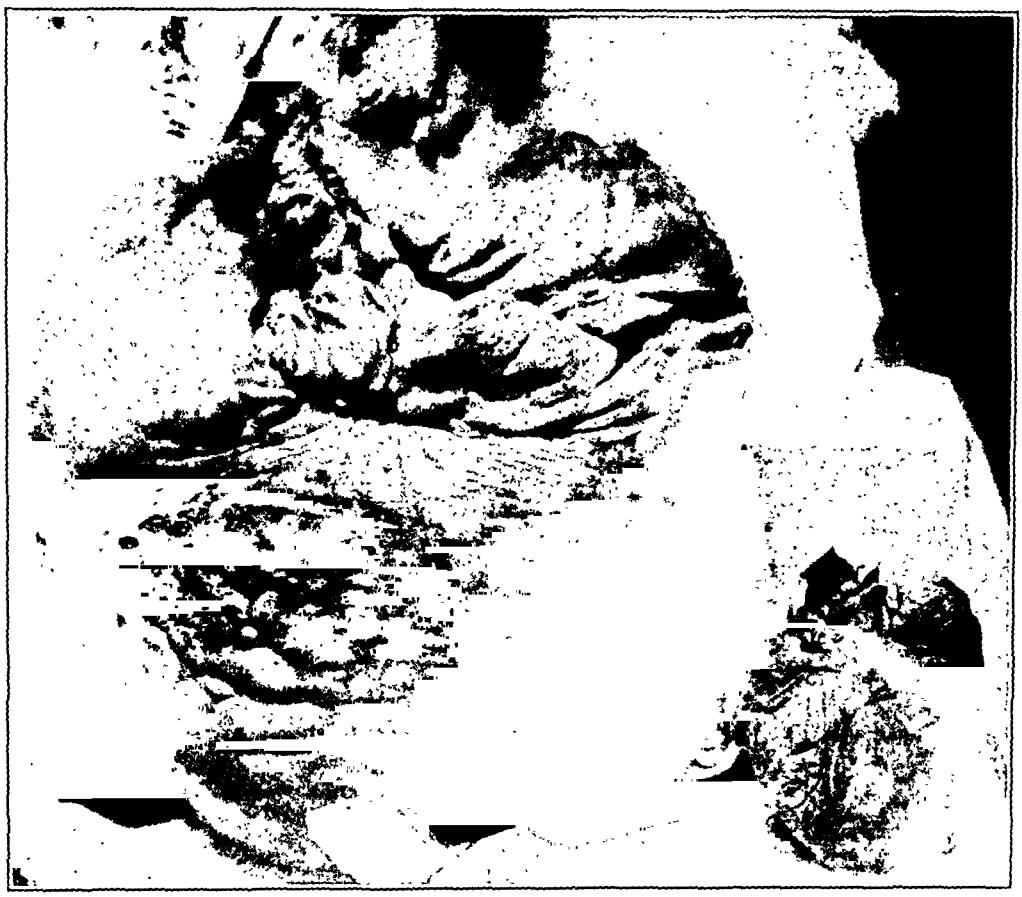

Fig. 1.—The frontal view of Mollie's heart with a normal adult human heart for comparison.

The heart muscle, valves, aorta, and coronary arteries were normal. There was no evidence of sclerotic change; there was one small milk spot on the pericardium. The sinoauricular and auriculoventricular nodes, as well as the auriculoventricular bundle, its branches, and the Purkinje network, were all visible beneath the endocardium. The sheath of the network was readily injected with India ink. The sinoauricular and auriculoventricular nodes and the auriculoventricular bundle and its branches were dissected.

Mollie's gross weight, as recorded at the Franklin Park Zoo, June 6, 1920, was said to be 8,180 pounds (3710 kg.). Her age at death was reputed to be 40 years.

CASE 2.—Tusko, a male Indian elephant, born in 1890, was brought into the United States when a relatively young animal. He was purchased from a small overland circus called M. L. Clark and Sons by Mr. Al G. Barnes, who exhibited him from the time of purchase in the early 1920's until May 24, 1931, when, on account of his tendency to rampage, he was sold, in Portland, Oregon, to another showman.[11] Later he was transported to Seattle. Here he was exhibited without license, kept heavily chained, and in unhygienic quarters, and inadequately fed. He was condemned by the City Health Authorities and placed in the Woodland Park Zoo on Oct. 8, 1932.

He had been proclaimed by Frank Buck and Lorenz Hagenbeck to be the largest Indian elephant in captivity,[11] and was renowned for his bad disposition. Measurements made at this time by the Park Authorities, and considered correct by the Superintendent of the Zoo, Dr. Gust Knudson,* were as follows:

Length, including trunk	18 ft.	11	in.	(577 cm.)
Height at shoulders	10 ft.	2	in.	(310 cm.)
Circumference of trunk		17½	in.	(44.5 cm.)
Circumference of foot at base		65	in.	(165 cm.)
Distance between eyes	2 ft.	9	in.	(84 cm.)
Total body weight said to be		14,313	lb.	(6491 kg.)

In the zoo Tusko was the most prized possession and accordingly received the best of care. Exercise was afforded by a one mile walk twice a week. The food consisted of hay, vegetables, and grain. Particular precaution was taken to avoid annoyance by visitors. He remained in the zoo throughout the fall, winter, and spring, and no significant difficulties were encountered due to unrest. His health was good, and his appearance improved.

On June 9, 1933, the attendant noticed that the elephant took no interest in food or drink, and that he was standing with hind legs stretched backward. Later he sat on his haunches, and finally lay down on the left side. Dr. Knudson, upon examining the animal, noticed "some respiratory disturbance." At this time he would swallow oranges without masticating them. Fourteen of these were partially filled with aloes and administered. By the following morning marked purgation had been effected, and at 8 A.M. the elephant was standing and eating hay, apparently greatly improved. While thus engaged, he suddenly lay down on his left side, and after a few gasps he died. This was at 9:55 A.M., June 10, 1933.

*To Dr. Gust Knudson, Superintendent of the Woodland Park Zoo, and to the Seattle Park Board we are indebted for the specimen as well as most of the information concerning the history of this elephant.

Disputes as to ownership and responsibility for disposal delayed the autopsy, which was not completed until June 12, approximately forty-eight hours after death. There is no record of any of the organs having been weighed or described. The greater part of the carcass was taken to a fertilizer factory, the skin was placed in cold storage, where it has remained ever since, and the bones were preserved for mounting.

Fig. 2.—Interior of Tusko's left ventricle. Note the thick ventricular walls, the heavy papillary muscles, the leaflets of the mitral valve, and the chordae tendineae.

When the heart was removed from the thorax, the cavities were explored and emptied through the great vessels. A large, hard, irregular fibrin clot was removed from the left ventricle. This mass was grayish-white, friable, and irregular in outline. It was not attached to the walls of the chamber. The measurements of the clot were 15¾ in. (40 cm.) x 7 in. (18 cm.), and its weight was 34 oz. (966 gm.). The clot was preserved in alcohol. Three veterinaries who witnessed this examination

thought that the clot had formed ante mortem and was the cause of death, with probable embolism to the brain or some other vital organ.

Post-mortem degenerative changes were progressing rapidly when the heart was examined 48 hours after death. It had become flabby and almost black in color. The pericardial surfaces were all smooth and of silken texture. The chambers were empty of blood. Both coronary orifices easily admitted three fingers. The weight was 48 pounds and 4 ounces (21.9 kg.). The specimen was embalmed with formalin by injec-

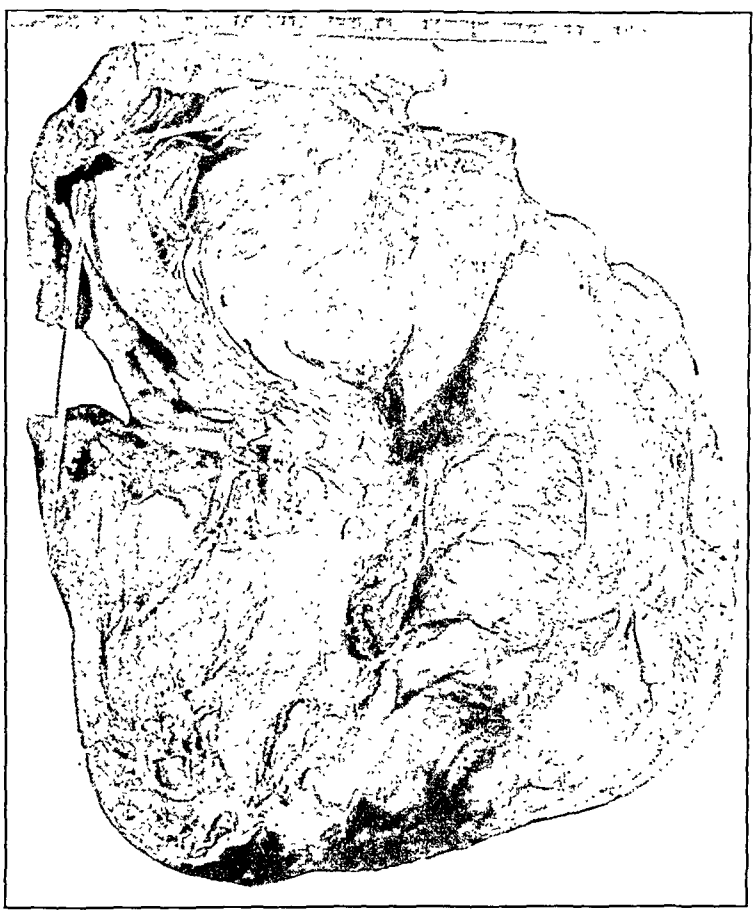

Fig. 3.—Interior of Tusko's right ventricle. Note the thinner muscular walls and lesser degree of papillary muscle development as compared with that of the left ventricle (Fig. 2). The chordae tendineae have been severed and the endocardium removed from the lateral portion of the ventricle. The broad leaflets of the tricuspid valve are seen at the upper left. Cross-section of a coronary artery appears at the extreme upper left.

tion of the coronary arteries under pressure of gravity; however, about one-fourth of the muscle mass could not be penetrated by the solution. It was then placed in a solution of formalin *in toto* and left for several months.

Examination of the heart by one of us (King) was completed in November, 1933. Post-mortem changes had obviously advanced to a moderate degree before embalming. There were a number of soft friable

areas in each ventricle where the preservative had not penetrated. The pericardium appeared normal. There was no apparent hypertrophy or dilatation of the ventricles, and there was no sclerosis of the aorta or coronary vessels.

The exterior surface of the entire right ventricle was covered with a subepicardial layer of fat varying from 1 to 2 cm. in thickness. The borders of this fat were sharply defined at the interventricular sulci,

Fig. 4.—Interior of Tusko's left ventricle and left auricle. Note the walls of the aorta above.

which it filled. This layer of fat was continuous with that filling the coronary sulci. Removal of the fat at the apex of the heart revealed the bifid appearance described by others. Fat was conspicuously absent from the surface of the left ventricle.

The endocardium appeared normal and overlaid a very thin layer of fatty tissue. The valves were of normal structure and apparently competent. The edges of the leaflets were smooth and presented no evidence

of sclerosis. The chordae tendineae and papillary muscles presented no evidence of excessive fibrous tissue deposit. For views of the interior of the ventricles see Figs. 2 and 3.

The left coronary artery originated from the apex of a funnel-shaped left ventral sinus, which admitted three fingers. The first portion passed for a short distance between the pulmonary artery and the left auricle. It then divided into its two terminal branches, the interventricular and the circumflex arteries.

The origin of the right coronary artery was from the right ventral sinus, which was less funnel shaped and shallower than the left. The first portion was in close relation to the aorta and then extended along the coronary sulcus, partially encircling the right auricle, giving rise to several small branches along its course. At the posterior interventricular sulcus it terminated in a descending interventricular branch and a smaller transverse branch. The latter crossed the posterior sulcus and terminated in branches to the basal portion of the left ventricle. We did not find a third, or *atrial,* artery arising from the aorta as described by Hill.[2]

The muscular wall of the left ventricle was thicker than that of the right. The average thickness of the interventricular septum was greater than that of either of the lateral walls (Table III).

TABLE III

MEASUREMENTS OF HEART (TUSKO)

Weight of heart	21.9 kg.	(48¼ lb.)
Outside circumference of aorta (22 cm. from semilunar valves)	23.0 cm.	
Average thickness of wall of aorta	1.52 cm.	
Average thickness of wall of pulmonic artery	1.3 cm.	
Average thickness of wall of left ventricle	4.08 cm.	
Average thickness of wall of right ventricle	2.05 cm.	
Thickness of interventricular septum	6.0 cm.	
Circumference of mitral valve	36.9 cm.	(14½ in.)
Circumference of tricuspid valve	38.1 cm.	(15 in.)
Circumference of aortic valve	27.9 cm.	(11 in.)
Circumference of pulmonic valve	22.9 cm.	(9 in.)
Diameter of left coronary artery		
At orifice	2.0 cm.	
Interventricular branch	1.2 cm.	
Diameter of right coronary artery		
At orifice	2.0 cm.	
Circumflex portion	1.5 cm.	

The aorta and pulmonary artery were soft and elastic, the wall of the former being almost twice as thick as that of the latter. There was no evidence of sclerosis or calcium deposit in either.

The sinoauricular node measured approximately 1 x 2 cm. The auriculoventricular node, the bundles, and the Purkinje system could not be clearly outlined on account of the degenerative changes. Measurements

of the interior of the heart, made in November, 1933, approximately five months after death, were as given in Table III.

Histologic study of the muscle, valves, aorta and neuromuscular tissue was attempted but was unsuccessful on account of degenerative changes. The only detail of structure discernible was that the cells were of large size and contained nuclei of corresponding size.

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ADDENDUM

In a very recent paper, his second on studies of the cardiac anatomy of the elephant (II. The Heart and Great Vessels of a Foetal Asiatic Elephant. Ceylon J. Sc., Section B, Zoology and Geology, 21: 45, 1938), W. C. Osman Hill found that the fetal heart (slightly older than midterm) described in this latest contribution agrees in all essential particulars with the hearts of adult animals of the Asiatic species.

"Its study has resulted in the emergence of further evidence regarding the very primitive nature of the organ, to the extent that it can definitely be stated that, in this advanced fetus, the heart, and related parts of the circulatory system, are in a state of development similar to that found in a human embryo of the fifth week of intrauterine life. Moreover, most of the embryonic characters in the proboscidean heart are known to be retained even in adult life, at least in some degree. Among the primitive features concerned are factors relating to form, shape and structure, and special attention may be directed to (i) the great transverse breadth of the organ relative to its other dimensions, (ii) the relatively large size and globular form of the ventricles, (iii) the apical bifurcation, (iv) certain arrangements in the interior of the right atrium, (v) the absence or incipient nature of the atrial appendages, and (vi) the poor differentiation of the papillary muscles.

"Besides these primitive features in the heart itself, a number of others, connected with more distal parts of the circulatory system, demand attention. Such are (i) the close connection of the systemic and pulmonary aortae, (ii) the simple curved form of the 'descending' aorta, (iii) the mode of branching from the transverse

part of the systemic aorta, (iv) the presence of a left precaval vein, (v) the disposition, etc., of the postcaval vein, and (vi) the arrangement of the azygos system of veins.

"(2) The atrial artery would appear to be a constant structure on the heart of the Asiatic elephant, having now been recorded in two adults, as well as in the fetus. There seems to be some variation in its mode of origin, but its distribution is much the same in all cases. Ideally this vessel takes the largest share in the formation of a more or less complete arterial ring which surrounds the roots of the great arterial stems as they emerge from the heart. The ring is completed ventrally, as far as it can be said to be complete, by the arch formed from the infundibular branches of the right coronary and ventral interventricular arteries. These last two vessels were not demonstrable in the fetal heart, but are well developed in the adult. They do not, however, form a complete arch, as they do on the human heart, for they form no precapillary anastomosis."

THE ELECTROCARDIOGRAM OF THE ELEPHANT*

PAUL D. WHITE, M.D., JAMES L. JENKS, JR., A.B., AND FRANCIS G. BENEDICT, PH.D., BOSTON, MASS.

IN THE course of a study of the physiology of the elephant an opportunity presented itself in the spring of 1936 to obtain a series of electrocardiograms from a number of circus elephants during their visit to Boston. Although the determination of the heart rate under different conditions was the primary reason for taking the electrocardiograms, the tracings themselves proved of such interest that they have been made the subject of the present report. Data on the elephant's heart rate have been published a number of times in the past.[1, 2, 3] Benedict and Lee[3] found that the rate averaged close to 40 per minute, with a normal range from 30 to 50, and occasionally was less than 30 or exceeded 50; the rate in a given elephant tended as a rule to be slightly lower when the animal was in the standing position than when recumbent (perhaps because the animal is more comfortable when standing, or because that position facilitates blood flow), although there were frequent exceptions due to various stimuli, such as noise or other commotion.

In 1921 Forbes, Cobb, and Cattell[4] took an electrocardiogram of a circus elephant that was visiting the Children's Hospital in Boston. The tracing they obtained was unsatisfactory because of the high resistance of the elephant's hide, the very small complexes of the record itself, and the high speed of the camera, which had been used for electromyography. However, a skillful reconstruction of their electrocardiogram, so that it conforms in amplitude and in timing to the usual standards, allows us to make a direct comparison with our own tracings. The heart rate of the elephant studied by Forbes, Cobb, and Cattell averaged 41, the duration of systole as measured by the interval from the beginning of Q to the end of T was 0.6+ second (the end of T was made out with difficulty), the QRS wave duration was about 0.15 sec., and the P-R interval was about 0.35 sec. These measurements are in fairly close agreement with our own.

Present Series.—During May, 1936, when the Ringling Brothers Circus was performing at the Boston Garden, one or more electrocardiograms were obtained by string galvanometer or by cardiette (mirror type galvanometer with amplifier) from each of the following nine elephants: Juno, Modoc, Tillie, Myrtle, Lizzie, Clara, Queen, Pigmy, and one unknown. The electrodes consisted of thin German silver plates covered with large cloth pads saturated in concentrated salt solution. The elephants were induced to step on these pads, which were simply laid on the cement floor over rubber mats. When the elephant was lying down,

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the pads were applied to the bottoms of the feet by an assistant. Because of the docility of the elephants, less difficulty than might have been expected was experienced in making connections. Remarkably low resistances (all well below 1,000 ohms and frequently in the neighborhood of 200 or 300 ohms) were invariably obtained from this procedure. Lead I was taken in all cases and often repeated; Leads II and III were occasionally taken also. The curves were sometimes smooth but more often slightly irregular in the base line, rendering it somewhat difficult to demarcate accurately the beginnings and endings of a number of the complexes which were themselves often not at all sharp. An example of the

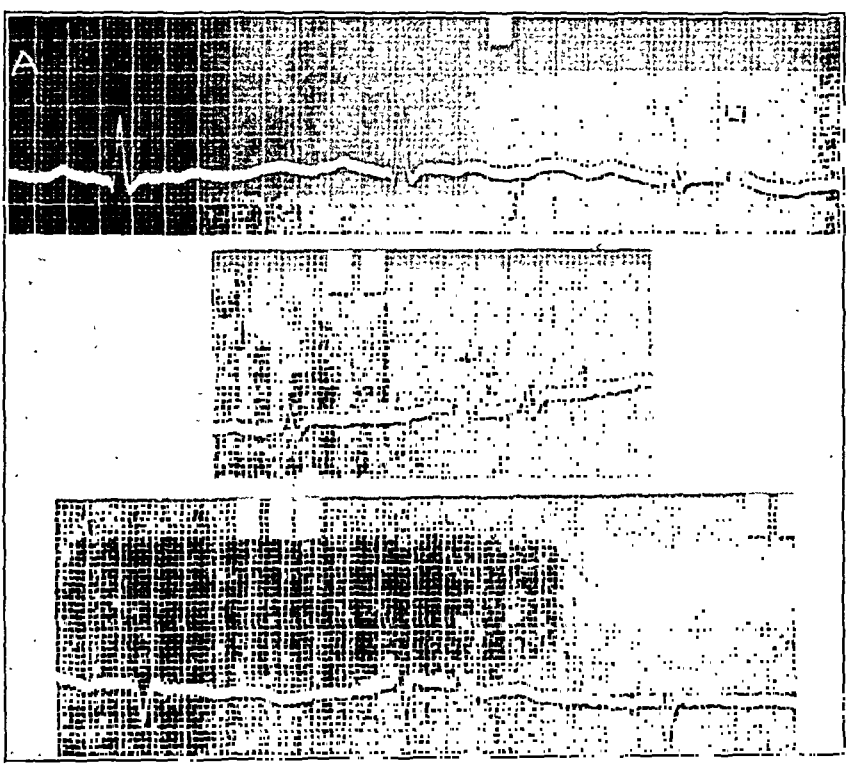

Fig. 1.—Electrocardiograms of the three classical leads of elephant Modoc. Time intervals, as also in Figs. 2 and 3: 0.2 and 0.4 sec. Amplitude: 10 spaces = 1.0 millivolt.

three leads of Modoc is shown in Fig. 1 and records of Lead I of Clara, Lizzie, and Juno are shown in Fig. 2.

Table I gives a description of the individual complexes and time intervals studied and measured in the best tracings of the nine elephants named above. It will be of interest and value to summarize the main features herewith.

P-Wave.—The P-waves of the elephants' electrocardiograms were invariably of low amplitude and were best marked in Lead I, which is in contrast to the findings in human electrocardiography with the subject in the sitting position. The amplitude in Lead I averaged about 0.1 millivolt (1 mm. excursion) with limits of 0.5 and 1.5 mm. In Lead II the P-waves tended to be flat, and in Lead III, slightly inverted.

TABLE I

DETAILS OF ELECTROCARDIOGRAMS OF ELEPHANTS (TIME INTERVALS IN SECONDS)

SUBJECT	LEADS	P-WAVE	P-R INTERVAL	QRS WAVE	Q-T TIME	T-WAVE	AXIS DEVIATION	RATE PER MINUTE
Modoc	I	Low, long domed	0.39	Small Q and S, R = +8. Dur.* = 0.18	0.62	Very low and long	Slight left	37.5
	II	Low, long domed		Small R and S. No Q		Flat		
	III	Flat		Small R, larger S		Sl. inverted		
Modoc	I	Higher, 1½ mm.	0.33	Q = −1, R = +8, S = −3, wide. Duration = 0.18	0.62	Higher, 1½ mm.		38
Modoc	I	Low, 1 mm.	0.38	Same. Dur. 0.18	0.64	Same		34
Modoc	I	Same	Same	Same		Same		Same
Tillie	I	Low, 1 mm.	0.37	Wide, monophasic R. R = 9 mm. Dur. = 0.16	0.60	Very low, sl. diphasic down and up		42
Tillie	II	Very low = ½ mm.	0.36	+3. Dur. = 0.13	0.70	Very low, late dome		36
Myrtle	I	+1½. Dur. = 0.16 and then flat 0.20	0.36	+4–½. Dur. = 0.12	0.60	Low, late dome, +1 mm.	Slight left	34 up and awake
Myrtle	I	−½ + 1. Dur. 0.16	0.40	+4. Dur. = 0.12	0.76	Sl. inverted −½		28 asleep
Juno	I	Low, 1 mm. Dur. = 0.2	0.36	−½ +8–2. Dur. = 0.16	0.79	+1 −0 +2. U present		26
Juno	I	Low, 1 mm. Dur. = 0.2	0.36	+8–2. Dur. = 0.16	0.76	+½–0 +2		24
Clara	I	Low, ½ mm. Dur. = 0.2	0.36	+5–2. Dur. = 0.12	0.60	Low late, 1 mm.		35
Pigmy	I	Very low, +½ mm.	0.28	+4–1. Dur. = 0.14	0.60	Very low, +½ mm.		39
Queen	I	Low +½-1. Dur. = 0.2	0.36	+8–1. Dur. = 0.15	0.68	S-T sl. sagging, low late T = 1	Slight left	36
Lizzie	I	Small early, +½-1. Dur. = 0.12	0.41	+7–2. Wide S. Dur. = 0.18	0.72	Sl. S-T sag, sl. late dome, ½		33
Lizzie	I	Same	0.35	Same	0.59	Same and followed by U-wave		53
Unknown	I	+1	0.38	−1 +8. Dur. = 0.14	0.65	Domed +1 mm., flat, sl. inverted	Slight left	33
	II	Small		+3				
	III	Flat		−8 +2				

*Dur. = duration.

The shape of the P-waves was as a rule that of a low dome or blunt peak, at times slightly diphasic with a very small early dip before the rise.

The duration of the P-waves ranged from 0.12 to 0.20 sec., averaging 0.16 sec.; after the end of P the baseline remained level for about 0.20 to 0.25 sec. before the onset of the QRS waves.

There was little change in amplitude, shape, or duration with varying heart rates although there were not enough records at different rates in any one animal to draw clear conclusions concerning this point.

P-R Interval.—The P-R intervals ranged from 0.28 to 0.41 sec., averaging 0.36 to 0.37 sec. In one animal (Lizzie) the interval varied with

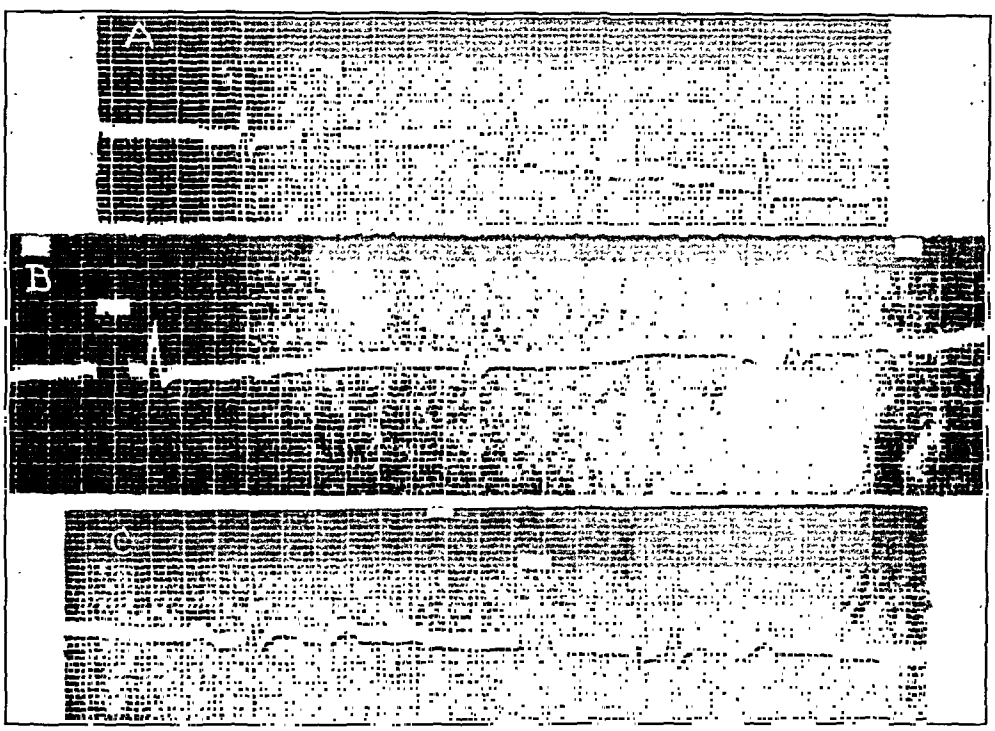

Fig. 2.—Electrocardiograms of Lead I of three elephants, Clara, *A*, Lizzie, *B*, and Juno, *C*, respectively.

the heart rate, as might be expected; it was 0.35 second with the unusually rapid heart rate of 53, and 0.41 sec. at a rate of 33.

QRS Waves.—The QRS waves, like the P-waves, were invariably of greatest amplitude in Lead I, in which the R-wave averaged about 6 to 8 mm. and the S-wave 1 to 2, with or without a very small Q wave (usually present). The S-wave in Lead I was often, in fact generally, the widest part of the complex.

The duration of the QRS wave was 0.16 sec., on the average, with a range from 0.12 to 0.18 sec. There seemed to be no relation of the QRS duration to heart rate.

In Leads II and III the QRS waves were always smaller than in Lead I; they were largely upright in Lead II and usually inverted in Lead III.

Thus there was, in the four animals from which three leads were obtained, consistent evidence of slight left axis deviation.

S-T Segments.—The S-T segments varied somewhat from animal to animal, averaging, however, little or no deviation from the zero base line. At times there was a slight convexity and at times a slight concavity, but often a straight line. The take-off from the QRS waves was neither high nor low.

T-Waves.—The T-waves were as a rule late, low, and of greatest amplitude in Lead I, where they varied from +0.5 to +2.0 mm. In Lead II they were low or flat, and in Lead III flat or very slightly inverted.

The shape of the T-waves was generally that of a long dome, rarely that of a sharper peak. At times they were slightly diphasic with an early sagging. In one case (Myrtle, see Fig. 3), the T-waves in Lead I

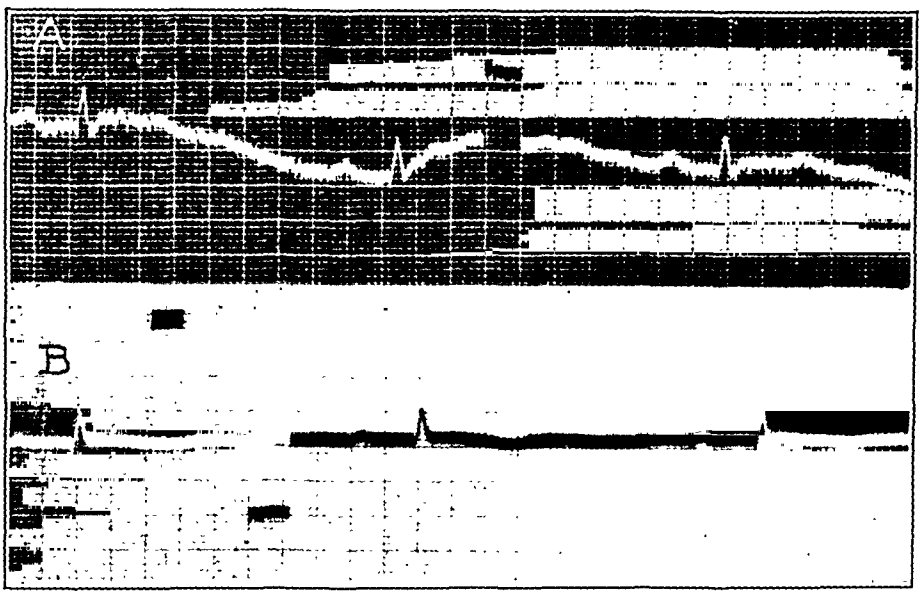

Fig. 3.—Electrocardiograms of the first lead of elephant Myrtle. *A*, standing, awake. *B*, lying down, asleep.

changed from late, low, dome-shaped elevations (1 mm. high) when the animal was standing and awake, to long, slightly inverted, troughlike depressions (0.5 mm. deep) when the animal was lying on her side asleep; the P-waves and to a less extent the QRS waves were also lower in the record taken with the animal recumbent. A change in heart position relative to the electrodes was probably primarily responsible for these electrocardiographic changes.

In a few records small U-waves followed the T-waves.

Q-T Times.—The duration of systole, as measured by the time interval from the beginning of Q to the end of T, varied from 0.59 to 0.79 sec., averaging 0.65 sec. It varied with the heart rate, as would be expected; thus the shortest Q-T time (0.59 sec.) was found in Lizzie when her heart rate was 53, the fastest encountered in the present series of records, while the longest Q-T times (0.76 to 0.79 sec.) were found in the only

two elephants whose records showed heart rates below 30 (0.76 second in the case of Myrtle with a heart rate of 28, and 0.76 and 0.79 sec. in the case of Juno whose rate was 24 to 26). Lizzie's Q-T time varied from 0.59 sec. at a heart rate of 53 to 0.72 sec. at a rate of 33.

DISCUSSION

The points of particular interest in the foregoing analysis of electrocardiograms of circus elephants are (1) the relatively low amplitude of all the complexes (P-, QRS, and T-waves) in the three classical leads, with greatest excursion in Lead I, and (2) the unexpected length of the various time intervals (P-R interval, QRS wave, and duration of systole as measured from the onset of the QRS wave to the end of the T-wave).

Neither artifact nor disease can explain the low amplitudes which are evidently characteristic of elephants' electrocardiograms. Although it is possible that there is a fairly close balance of electrical potential in the heart muscle at all times, it is more likely that the small difference of potential is due to the long distances of the heart mass itself from the junctions of the legs to the trunk; comparably, it is well known that in man an electrocardiogram taken from lead points on the legs shows very small complexes.

Some of the undue length of the P-R interval and Q-T time might be ascribed to the bradycardia, but the delay is out of all proportion to the heart rate if we compare the findings in human electrocardiography at such slow rates of contraction; in man with sinoauricular bradycardia at a rate of 40 the P-R interval might normally be 0.2 sec., but never nearly double that, as in the case of the elephant, and the Q-T time in man at a heart rate of 40 might be 0.4, or even 0.45 sec., but never as great as 0.6 to 0.7 second as in the elephant. It would appear that the great size of the elephant's heart may best explain the P-R interval and Q-T time as well as the unusual width of the QRS wave (0.1 to 0.2 sec). It is important to note that, as described by King, Burwell, and White,[5] the heart muscle, nodal tissue, and Purkinje network are the same as in other herbivorous mammals.

SUMMARY

An analysis has been made of the electrocardiograms of nine circus elephants with heart rates ranging from 24 to 53 per minute (average of 35 to 40).

Relatively low amplitude of the P-, QRS, and T-waves was found in the three classical leads (with greatest excursions in Lead I), despite accurate standardization which was made easy by the remarkably low resistance invariably found (often only 200 to 300 ohms in any given lead).

The various time intervals (P-R of 0.28 to 0.41 sec., QRS of 0.12 to 0.18 sec., and Q to T time—duration of systole—of 0.59 to 0.79 sec.) were

beyond the measurements to be expected at slow heart rates in the case of mammals of average size like man, and may be explained by the immense size of the elephant's heart with its longer paths of impulse conduction and its greater bulk of contracting muscle.

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Department of Clinical Reports

PERFORATION OF THE INTERVENTRICULAR SEPTUM CAUSED BY CORONARY OCCLUSION

Report of a Case

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PERFORATION of the interventricular septum is an uncommon complication of coronary occlusion. To date twenty cases in which its occurrence has been verified have appeared in the literature. Of these only three have been diagnosed correctly ante mortem (Brunn,[1] Sager,[2] and Stanley[3]). It is our purpose to report the fourth case to be diagnosed before death and to point out that Sager has set forth criteria which if borne in mind will lead to accurate diagnosis in a higher percentage of cases.

CASE REPORT

Mrs. M. B. J., a widow, aged 70 years, first came to us on Jan. 14, 1938, because of a tracheitis of several weeks' standing. Examination of the heart at that time showed nothing abnormal. The blood pressure, however, was 160/100.

On the morning of Jan. 19, 1938, the patient was awakened by a severe, devastating pain between the shoulder blades, radiating down both arms, to be followed a bit later by distress over the lower precordium. When first seen by us at 11:00 A.M. of the same day, severe pain had persisted and was accompanied by sweating. She was obviously very ill. The pulse rate was 96 per minute, the blood pressure 190/110. The heart sounds were muffled. One 1/100 of a grain of nitroglycerin under the tongue gave some relief from the precordial pain but that between the shoulders was unaffected. Both pains finally yielded to morphine sulfate hypodermically, first in the dose of ¼ grain and somewhat later, one ⅓ grain. On the evening of the day of onset the blood pressure had dropped to 140/90. At noon the temperature per rectum was 100° F. On the morning of January 20 the pulse rate was 120, the blood pressure 100/80. The heart had enlarged to the left at the apex. There was a faint apical systolic murmur and gallop rhythm had appeared. Moist râles were found at both bases. At midnight the rectal temperature was recorded at 103.6° F. The patient vomited repeatedly and intermittently suffered pain between the shoulder blades. Prostration was an outstanding symptom and increased as time went on. On the third day, January 21, the patient was much worse. The blood pressure was now 88/74. Tachycardia developed and ranged from 120 to 158 with many premature contractions. Quinidine sulfate, in doses of 3 grains every four hours, was started to forestall the development of ventricular fibrillation. Gallop rhythm persisted. The rectal temperature was constantly elevated and ranged from 102.2° to 102.8° F. Laboratory data were

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as follows: The hemoglobin was 83 per cent (12.5 gm. per cent); the erythrocyte count, 4,460,000; the leucocyte count, 11,300; and the differential leucocyte count showed 76 per cent polymorphonuclears (lobulated 67 per cent and band forms 9 per cent). The sedimentation rate was 55 mm. in one hour (Wintrobe Normal 0-20.) An electrocardiogram (Fig. 1) confirmed the initial clinical impression of acute coronary occlusion but did not definitely place the site of infarction, though it suggested a lateral wall involvement (Lead IV was made with the right arm lead at the apex and the left arm lead over the left side of the chest posteriorly). On January 22, the fourth day of the illness, the patient showed considerable improvement. She was no longer bothered by pain. Vomiting ceased. The rectal temperature was lower (100.4° to 101.6° F.). The pulse rate slowed to 100 and the blood pressure increased to 100/80. Satisfactory progress continued. On the seventh day, January 25, the rectal temperature ranged from 99.6° to 100.2° F., the

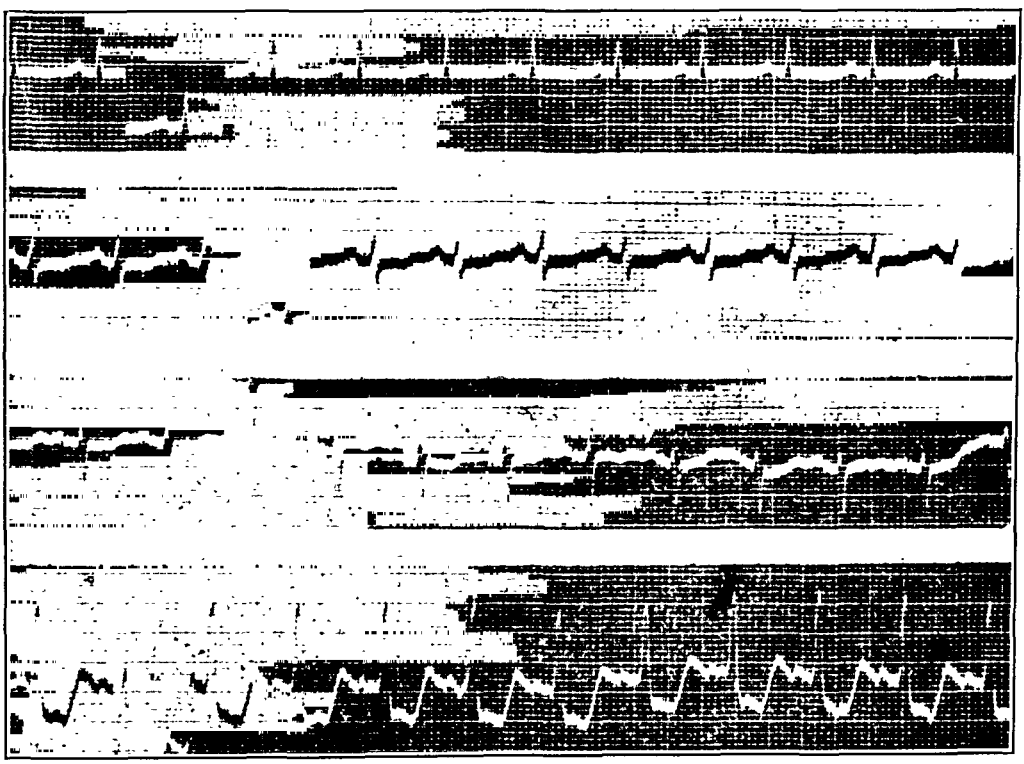

Fig. 1.—Electrocardiogram made on the third day of the illness. Lead IV is inscribed from anterior and posterior chest connections, according to the old technique. See text for interpretation.

pulse rate from 90 to 100, and the blood pressure in the morning was 105/70. However, at 5:00 P.M. she complained of return of the precordial pain and oppression as well as pain under the left shoulder blade. Intermittently during the night she was nauseated and at 9:00 P.M. she vomited. All of the symptoms and particularly the pain were mild in comparison with those suffered at the time the occlusion developed. Examination the next day, January 26, revealed important changes, and in view of subsequent findings it is necessary to describe the situation in some detail. The patient was free of pain, complaining only of marked weakness. No increase in dyspnea or cyanosis was noted. There was no engorgement of the neck veins. The pulse was 112 to the minute, regular, but of fair quality only. The blood pressure had dropped to 88/68. There was no apparent increase in the heart size to the left. Unfortunately, the limits of the right border were not determined at this time. No thrills could be palpated at any point. Most remarkable were the auscultatory findings. Over the entire precordium there was

a loud, high-pitched, blowing systolic murmur, most intense in the left parasternal region in the fourth and fifth intercostal spaces, where the murmur was slightly rasping in character. Transmission was wide both to the left and to the right and even into the back and epigastrium but the intensity of the new murmur was by far most marked toward the apex and the left axilla. The second heart sound was faint and in many of the cycles there was a protodiastolic gallop rhythm. No murmur could be heard in diastole. The obvious changes in the picture were ascribed to spontaneous rupture of an infarcted interventricular septum. Bedside notes made during the next four days indicate that there were no radical changes in the patient's circulation. The fact that there were less dyspnea and fewer râles suggested that pulmonary congestion was diminished. The rectal temperature level was practically stabilized at 100° F. The blood pressure ranged from 80/60 to 92/75, and the pulse pressure from 17 to 20. On January 31, six days after the perforation, the edge of the liver had descended to a point 5 cm.

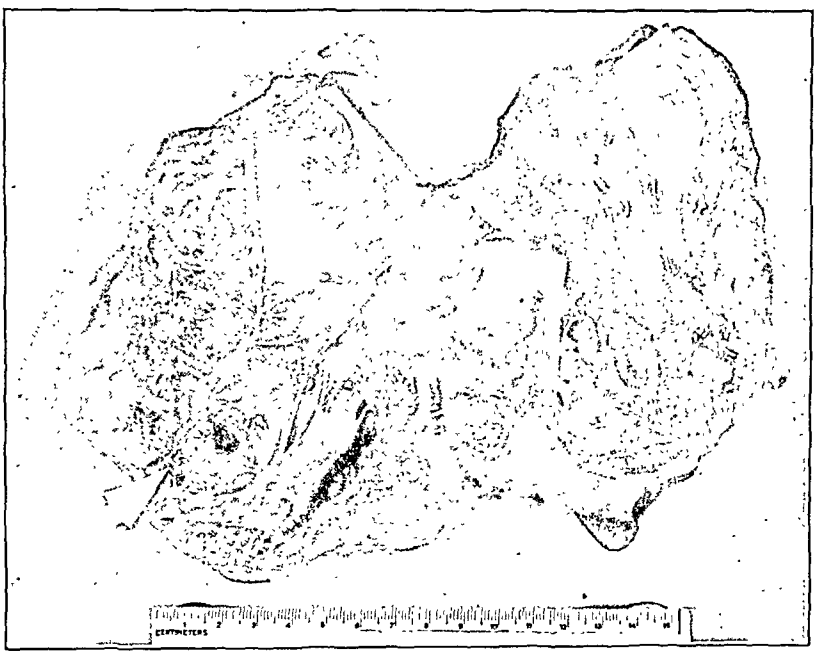

Fig. 2.—Photograph of the heart. The arrow points to the perforation of the interventricular septum. See description of pathologic findings.

below the costal margin, and on the next day, 8 cm. Administration of digitalis was followed by temporary lessening of hepatic congestion. On February 6, twelve days following the perforation, edema appeared over the lower part of the back. The course thereafter was one of increasing congestive failure. Death ensued on February 12, fifteen days after the perforation and on the twenty-fifth day of the illness.

NECROPSY OBSERVATIONS CONCERNING THE HEART AND AORTA*

There was a rather diffuse thickening of the aortic wall for the first few centimeters, above which point scattered, nodular, atheromatous patches, occasionally calcified, were more evident.

The coronary orifices were patent, measured about 1.5 to 2 mm. in diameter, and were surrounded by a firm ring of somewhat pouting fibrous tissue. The aortic cusps were definitely thickened by fibrosis in the proximal one-third to one-

*By Dr. J. W. Lindsay, Pathologist.

half. The outer edges were thin and the valves appeared to be quite competent. The endocardium of the left ventricle was somewhat thickened as indicated by its slight spasticity. Yellowish plaques and dots were seen in the papillary muscles and scattered diffusely through the myocardium. A large area of evidently degenerated muscle, mottled in color and rough in appearance, was noted in the interventricular septum, in the upper border of which a perforation measuring 1 by 0.5 cm. was observed. On dissection of the left coronary artery, which was found to be markedly calcified, there were several fairly large branches penetrating to the border of the area of degeneration described. While the right coronary artery was patent for a greater distance than the left, it also was markedly nodular and fibrosed, and the posterior descending branch was completely occluded in the neighborhood of the degenerated area of the septum. The wall of the right ventricle was much thinned and the changes in the musculature, while similar to those in the left ventricle, were not so evident. All valves showed some degree of sclerosis though all appeared to be competent.

SUMMARY

This is a report of the twenty-first case of perforation of the interventricular septum caused by coronary occlusion in which the presence of this lesion was verified, and the fourth in which a correct diagnosis was made ante mortem.

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Department of Reviews and Abstracts

Selected Abstracts

Hessel, G.: Concerning Renin. Klin. Wchnschr. 17: 843, 1938.

The author has obtained Tigerstedt's renin in a yellow amorphous powder pure enough for 0.1 mg. to give a good rise of pressure (40 mm. Hg) in a 9 kg. dog. It was obtained by pressing out the juice of hog kidney (also beef, dog, cat, and rabbit), dialyzing it against running water, which rid it of depressor effects, and precipitating it during a period of a day in acetic acid solution (pH 4.4) saturated with sodium chloride. The salt was then dialyzed off, the pressor substance dissolved in 2 to 5 per cent sodium chloride solution and filtered; filtrate was acidified with lactic acid (pH 3.4); and the substance adsorbed on kaolin, from which it was freed by making the solution faintly more alkaline than other adsorbed substances. The renin was then freed from pigments and electrolytes by ultrafiltration and dried in an evacuated desiccator. It is soluble in water and weak sodium chloride solution, insoluble in and destroyed by organic solvents. It is also destroyed by mineral acids and alkali, by heating to 65°, and by pepsin or trypsin. Its molecular weight is high, it is not dialyzable and is precipitated by concentrated salt solutions, and gives protein reactions.

The rise in arterial pressure which follows intravenous injection of 0.2 or even 0.1 mg. is slow (maximum in 2 to 5 min.) and takes from 15 to 60 minutes to subside. It does not affect heart rate, and the author states that it does not increase the amplitude of the pulse. However, in the only optical record shown, the pulse pressure increases roughly 10 mm. Hg, as is to be expected. It does not affect the isolated heart, the iris, bronchial muscle, or uterus. The marked differences in action between renin and other pressor substances (tonephin, vasopressin, tyramin, adrenalin) are well shown in several records.

The author has obtained continuous hypertension in rabbits by daily injections of renin over a period of five weeks—a hypertension which persisted as long as seven months after discontinuing the injections.

He also shows two records of a rise of blood pressure (20 mm. Hg) in dogs following the injection of 3 c.c. of blood from the renal vein of a dog's kidney, the artery to which had previously been partially clamped.

STEELE.

Jochim, Kenneth: The Contribution of the Auricles to Ventricular Filling in Complete Heart Block. Am. J. Physiol. 122: 639, 1938.

From ventricular volume curves recorded simultaneously with aortic pressure pulses in a dog with complete A-V block, an analysis is made of the dynamics of each auricular beat. The effective auricular contribution to ventricular filling is defined and its magnitude correlated with the A_s-V_s interval. The effective auricular contribution is found to increase slowly as the A_s-V_s interval decreases. When this interval becomes equal to the duration of auricular systole, the auricular contribution begins to increase rapidly, reaching a maximum at an

A_s-V_s interval equal to about half the duration of auricular systole, and falling off sharply to zero as the interval further decreases. The factors affecting this correlation are discussed.

AUTHOR.

Katz, L. N., and Kolin, A.: The Flow of Blood in the Carotid Artery of the Dog Under Various Circumstances as Determined with the Electromagnetic Flowmeter. Am. J. Physiol. 122: 788, 1938.

A method is described for measuring cyclic variations in the velocity of blood flow in unopened blood vessels based on the induction of an E.M.F. in the blood when moving through a magnetic field. Cyclic variations in the velocity of blood flow through the carotid artery of anesthetized dogs were recorded with this D.C. method under various conditions, viz.: 1, with the anesthetized animal intact; 2, with the chest opened; 3, during rapid saline infusion; 4, during partial occlusion and after release of the thoracic aorta; 5, during aortic valve insufficiency in which an early diastolic back flow was demonstrated; 6, during marked cardiac arrhythmia; 7, during ectopic beats, and 8, during gasping respiration. The characteristics of the velocity curves in each case are described and their significance discussed.

AUTHOR.

Corwin, Warren C.: Experimental Hypercholesteremia in Dogs. Arch. Path. 26: 458, 1938.

The data obtained from the experiments indicate that a diet high in fat may or may not produce moderate hypercholesteremia in the dog. Lecithin of adrenal origin, when given by mouth daily, will constantly raise the concentration of cholesterol in the blood. Lecithin plus a diet high in fat will effect marked elevation of the level of the blood cholesterol and of cholesterol esters. Cholesterol and sodium cholate have no effect when administered by capsule in the solid state.

If the development of arteriosclerosis in the dog is dependent on the development of hypercholesteremia, as in the case of the rabbit, the studies reported indicate that perhaps the dog may yet be employed in the study of this disease.

NAIDE.

Hsi-Chun Chang, Kuo-Fan Chia, Ching-Hsiang Hsu and Lim, R. K. S.: A Vagus-Post-Pituitary Reflex. I. Pressor Component. Chinese J. Physiol. 12: 309, 1937.

In dogs in which vascular connection with only the head exists, the neck having been crushed (no mention of periarterial sympathetic resection) and vagi cut, it is possible to produce a pressor response in the systemic circulation by stimulating the central end of the vagus or the cervical sympathetic nerves. Removal of the pituitary gland or cutting its stalk prevents the pressor response to central vagal stimulation but not to sympathetic stimulation. The authors conclude that stimulation of the vagus nerve calls forth secretion of posterior pituitary principle by that gland's secretory nerves which then acts on the systemic arterioles directly. This view is opposed to the notion that the vagus pressor effect is brought about through stimulation of a sympathetic center in the hypothalamus.

STEELE.

Sabathie, L. Gonzales: Phonocardiographic Studies of Reduplication of the Second Heart Sound. Rev. argent. de cardiol. 5: 25, 1938.

The phonocardiographic picture of the second heart sound simultaneously recorded with the venous and central arterial pulses in sixteen cases of mitral stenosis with clinical reduplication of the second sound and variable degrees of evolution and

cardiac failure (two of them with auricular fibrillation), and in nineteen persons with physiologic reduplication of the second sound (eleven children from 5 to 12 years of age and nine young adults from 15 to 30 years of age) and, finally, in five patients with organic heart disease, showing marked disturbances of intraventricular conduction, all of them presenting clinical reduplication of the second sound, revealed that in a case of mitral stenosis the reduplication was simulated by an opening snap of the mitral valve, and in two young people by a physiologic third heart sound. In the rest of the cases a true reduplication was confirmed.

In all cases of mitral stenosis and physiologic reduplication the first component of the second sound corresponded in time with the aortic incisura, showing that the aortic valves closed in advance to the pulmonary, a fact against Potain's views assuming that the opposite was the case in mitral stenosis, but in agreement with his views so far as physiologic reduplication is concerned.

In four of the five cases of ventricular asynchronism, the first component of the second sound coincided with the aortic incisura (aortic precedence) and in the fifth, a pulmonary precedence was recorded.

AUTHOR.

France, Richard: The Use of the Electrocardiogram in the Diagnosis of Adhesive Pericardio-Mediastinitis. Bull. Johns Hopkins Hosp. 63: 104, 1938.

An analysis has been made of thirty-eight cases in which shift of the electrical axis was studied during life, and the hearts were examined at autopsy. No constant relationship was found between the fixation of the electrocardiogram and the presence of restricting pericardial adhesions. It is, therefore, concluded that the electrocardiographic test for "axis shift" is not of value in the ante-mortem diagnosis of adhesive pericardio-mediastinitis.

AUTHOR.

Robertson, Sylvan, and Katz, Louis N.: Observations on Referred Pain of Cardiac Origin. Am. J. M. Sc. 196: 199, 1938.

A method was developed for inducing an anginal attack in susceptible patients with their permission. This was successful in nineteen out of twenty-four patients with definite clinical angina pectoris. It was not successful in producing an anginal attack in any of the fifty-five cardiac and "noncardiac" controls nor in any of the thirty-nine patients with doubtful clinical angina pectoris.

The method consisted of producing five-minute ischemia in the left arm by raising the pressure in a blood pressure cuff on the arm to 50 mm. Hg above systolic pressure. This cuff test was positive on the right arm and not on the left arm in three patients in whom the pain was referred to this arm.

The possible mechanisms involved are discussed. The ability to induce angina in this way serves to emphasize the neuropsychic aspects of the anginal attack and offers another cause for the variability in its occurrence.

AUTHORS.

Misske, B.: Renal Insufficiency and "Pale" Hypertension on the Electrocardiogram. Arch. f. Kreislaufforsch. 2: 267, 1938.

Fifty-three cases of uremia and fifty cases of nephrosclerosis without evidence of renal insufficiency were investigated to see whether electrocardiographic changes are due to arterial spasm of the coronary arteries or to uremic intoxication.

In uremia all cases showed evidence of myocardial damage in the electrocardiogram, and 41 per cent showed more than one electrocardiographic abnormality. The chief abnormalities were flattening or inversion of T, low "voltage," and

intraventricular block. In nine cases studied more intensively, some parallelism of electrocardiographic changes and changes in the degree of uremia could be found. Therefore, electrocardiographic changes are due to "myodegeneratio uremica."

KATZ.

Eckey, P., and Fröhlich, R.: Concerning Unipolar Leads for the Electrocardiogram. Arch. f. Kreislaufforsch. 2: 349, 1938.

To obtain true unipolar leads the subject was immersed in distilled water bath contained in a wooden bathtub lined with copper. The subject lay on a wooden lattice with the head under water, the nose closed, and breathing through a glass tube. A copper lid was then placed over the patient and the indifferent electrode placed on this lid. It was shown that while Wilson's central terminal and Molz's copper mat were both not nul points, Wilson's central terminal approached the true nul point, showing deviation during the heart cycle of 0.2 to 0.3 millivolts.

KATZ.

Eckey, P., and Schäfer, E.: Deformation of the Ventricular Complex of the Human Electrocardiogram by the Action Currents of Abnormal Conducting Fibers. Arch. f. Kreislaufforsch. 2: 388, 1938.

A case is reported of an apparently normal patient with intermittent periods of beats with short P-R and prolonged QRS complexes. By algebraic subtraction of the normal QRST from the abnormal one, a small ventricular complex was obtained having its T-wave opposite to the broad QRS. This the author attributes to the action current generated in abnormal conducting tissue during the abnormal beats and believes this explains the peculiar type of record obtained.

KATZ.

Parkinson, John, Bedford, D. Evan, and Thomson, W. A. R.: Cardiac Aneurysm. Quart. J. Med. 7: 455, 1938.

The evolution of our knowledge of cardiac aneurysm and its morbid anatomy is shortly reviewed.

Cardiac aneurysms are usually due to coronary occlusion with resultant infarction, and rarely to syphilis, infective endocarditis, congenital defects, or trauma. A detailed necropsy report is given of a case ascribed to rheumatic necrosis of the myocardium.

Cardiac aneurysms, like infarcts, involve the left ventricle almost exclusively and may best be classified as anterior or posterior, according to the coronary branch occluded. The great majority involve the anterior wall of the left ventricle, usually at or near the apex.

The clinical and radiologic features of fifteen cases of cardiac aneurysm are described, and in five of them the diagnosis was confirmed by necropsy. The significant clinical features are a history of coronary thrombosis, enlargement of the heart to the left, a normal or low blood pressure, distant heart sounds, and an electrocardiogram most often indicative of anterior infarction (T_1 type). Expansile pulsation separate from the apex beat, or an extensive area of precordial pulsation, is rare but suggestive sign.

Diagnosis depends mainly upon radiologic examination. Anterior aneurysms cause enlargement of the heart to the left, with deformity of its contour. This deformity, seen from the front, may take the form of (1) broadening of the apex or angulation of the left border, giving the heart a square or rectangular appearance;

(2) elongation of the heart to the left; (3) a diffuse bulge or, more rarely, a localized hump on the left border. In the right oblique position, "ledging" of the anterior heart border is of great diagnostic value. Posterior aneurysms are best seen in the left oblique position, and may displace the esophagus. Aneurysm of the interventricular septum has been known to cause enlargement of the heart to the right. Calcification of the aneurysmal wall, when present, is an invaluable sign. Radioscopy is essential to determine the optimum position for demonstrating the aneurysm, to observe the character of the pulsation, and to detect localized adhesion.

The differential diagnosis has to be made from an enlarged right ventricular conus, aortic aneurysm, especially that involving a sinus of Valsalva, calcified pericardium, loculated pericardial exudate or cyst, the para-apical triangle of fat, and from intrathoracic neoplasm or cyst.

AUTHORS.

Read, Frances E. M., Ciocco, Antonio, and Taussig, Helen B.: The Frequency of Rheumatic Manifestations Among the Siblings, Parents, Uncles, Aunts, and Grandparents of Rheumatic and Control Patients. Am. J. Hyg. 27: 719, 1938.

This paper reports on the frequency of the occurrence of rheumatic infection (chorea, acute rheumatic fever, and rheumatic carditis) in the siblings, parents, uncles, aunts, and grandparents of thirty-three white children with rheumatic disease and of thirty-three white nonrheumatic children selected as a control. The method of the collection of the material and of the verification of the information is given in detail. It is shown that the rheumatic and control groups do not differ materially with respect to the age distribution, sex composition, mortality rate, or in regard to the character and accuracy of the information.

Statistical analysis of the data indicates that rheumatic manifestations were found to have occurred in 15.5 per cent of the siblings of the rheumatic patients and in 4.0 per cent of the siblings of the control patients.

Among the parents of the rheumatic patients, 30.8 per cent were found affected, compared to 7.7 per cent among the parents of the control children.

Some form of rheumatic disease has occurred in 9.1 per cent of the uncles and aunts of the rheumatic children and in 3.8 per cent of the corresponding relatives of the control children.

The frequency of rheumatic disease is almost eight times as high among the grandparents of the rheumatic patients as among the grandparents of the control children, the percentages being, respectively, 18.2 and 2.3.

All these differences are statistically significant and are corroborated by a marked difference in the calculated attack rate based on the life experience of each group of relatives.

The high frequency of rheumatic disease found among the parents and siblings of rheumatic children confirms the numerous observations reported by others. A similar prevalence of rheumatic disease found among the uncles, aunts, and grandparents appears highly significant. Between the patients and their siblings and parents there is usually contiguity as well as consanguinity, but the uncles, aunts, and grandparents of the patients, in the majority of cases, do not belong to the same household or to the same immediate environment. Their necessary and known relation to the patient is not that of sharing a common environment but only one of consanguinity and of common inheritance.

These findings, although not sufficiently definitive to determine the relative importance of heredity and environment, are indicative of the strong familial tendency to this disease. The fact that such a familial tendency has been manifest for at least three generations is strongly suggestive of the existence of a constitutional susceptibility to this disease. This does not eliminate the possibility that exposure is also an important factor.

The facts here presented, while not conclusive, clearly indicate the need for a more thorough study of (1) the epidemiology of this disease, especially with regard to the sequence between cases in the same family, and (2) the inherited predisposition, including a search for stable somatic characteristics which might be associated with susceptibility to rheumatic infection.

AUTHOR.

Allen, E. V., and Adson, A. W.: Answers to Some Objections to Extensive Sympathectomy for Essential Hypertension. Proc. Staff Meet., Mayo Clinic 13: 426, 1938.

An extraordinary interest in the treatment of essential hypertension by sympathectomy has developed. Concurrently with this interest, certain objections to the treatment of essential hypertension by sympathectomy have been broached. The objections most frequently stated are considered and answered for the purpose of clarification of the issues. Most of the theoretical objections have been shown not to be valid as far as humans are concerned by the results obtained following sympathectomy.

HINES.

Zinck, K. H.: Changes in Blood Vessels and Organs Following Burns. Klin. Wchnschr. 17: 278, 1938.

Microscopic studies of the tissues of eight youthful subjects who died of third degree burns showed many interesting changes. Some of these changes are, as the author admits, well known. The author notes especially localized swellings of the larger arteries around the vasa vasorum, which appear within twenty-four hours and progress through atrophy of both the elastic and muscular coats to fragmentation within three weeks. The muscular coats of the venous walls also participate in the process, and even in the aorta is affected to a milder degree. The lesions recall those reported to follow extreme use of adrenalin in man. The heart also is involved partly by a similar affection of the coronary vessels and partly in an apparently independent process consisting of edema and fatty degeneration of the fibers, often with considerable destruction of the contractile substance. All of the organs and tissues show pathologic changes; swelling and rupture of the striated muscle fibers; replacement of the normal white cells of the blood by youthful cells of the myeloid series and shrinking of the red blood cells; in the kidney, inflation, collapse and lysis of the glomeruli; hemorrhage into the capsular spaces, cloudy swelling and hyalinization of the tubules, occasionally severe panarteritis but always widespread edema. Somewhat similar changes, mostly involving edema are found in all the organs. Of especial interest is the disappearance of lipoid from the adrenal glands and the disappearance of the basophilic substance and pepton cells of the pituitary gland. The author wonders whether these changes might not be of importance in the lack of regulation of blood pressure. In concluding, he states that many of the pathologic changes are similar to those of acute infections, notably diphtheria, and decries the use of cortical extract in treatment when it is obvious that the adrenal gland is only one of the many organs involved.

STEELE.

Mészáros, K.: Oscillometric Studies of the Arteries in Scleroderma. Acta med. Scandinav. 95: 522, 1938.

Ten patients, suffering with scleroderma, uniformly showed decrease in the oscillometric index and in the more advanced cases, the curve was exceedingly

flat. Hot water baths (40° C.) did not increase the oscillometric readings, from which the author concludes that the elasticity of the arteries is decreased in this disease.

STEELE.

Whittaker, Louis D., and Pemberton, John deJ.: Mesenteric Vascular Occlusion. J. A. M. A. 111: 21, 1938.

In this series of sixty proved cases of mesenteric vascular occlusion, in thirty-six (60 per cent) the condition was unrelated to any surgical procedure and in twenty-four (40 per cent) it occurred following some surgical procedure. Surgical measures were resorted to in treatment of the occlusion in only nineteen cases (31 per cent) with a mortality rate of 84 per cent. The condition of the forty-one remaining patients precluded any hope of surgical intervention. Arterial occlusion occurred in nineteen cases (31.7 per cent), venous occlusion in twenty-seven cases (45 per cent) and combined arterial and venous occlusion in fourteen cases (23 per cent). Cardiac disease, hepatic or splenic disease, arteriosclerosis and acute abdominal infections were the predominant factors in the etiology of mesenteric vascular occlusion.

The symptoms were those of an abdominal emergency. Pain was the most common symptom and was more sudden and severe in arterial occlusion. Vomiting was frequent. Rigidity and tenderness were more common with arterial occlusion, while distention alone was more suggestive of venous occlusion. Bleeding from the bowel occurred decidedly more frequently in the cases of venous occlusion but occurred in only fourteen cases (23 per cent) of the series; it is a valuable diagnostic sign if present. The leucocyte count was elevated to higher levels than that usually encountered in the more frequent abdominal emergencies. The rapidity of progress, the extensiveness of the disease and the tendency for progression or recurrence following operation make for poor prognosis.

MONTGOMERY.

Farks, Harry: Aneurysm of the Innominate Artery. Arch. Int. Med. 61: 898, 1938.

Three cases of aneurysm of the innominate artery are presented. All these patients had syphilis, and all died by rupture of the aneurysm. Though in early cases prompt symptomatic relief is likely to be obtained by antisyphilitic therapy, the differential diagnosis with aortic aneurysm, presenting in the neck, is important. Aortic aneurysm presents no opportunity for surgical measures, whereas aneurysm of the innominate artery has been successfully treated by surgery. None of the author's cases were treated by surgery.

MONTGOMERY.

Salatich, Peter B.: Varicose Veins of the Broad Ligament and Their Consequences. South. M. J. 31: 697, 1938.

Patients who complain of back pain, especially that relieved by resting and associated with menstrual disturbance, should be studied for possible varicose veins of the broad ligament. Diagnosis is made during pelvic examination by passing the examining fingers to the sides of the cervix, keeping in line with the axis of the uterus, pressing upward in the parametrium. If enlarged veins are present, this will cause considerable pain. Generally, the cervix is softer than normal and the body of the uterus boggy to feel. To eliminate the possibility that the ovaries or tubes are the cause of the trouble, the finger is directed

anteriorly and upward. If the tube and ovary are found not enlarged or painful, the veins are the probable cause of the trouble. The author presents a conservative operation of combined ligation of these veins and uterine suspension. He says this gives relief whereas suspension alone does not.

MONTGOMERY.

Hoenig, J.: Thromboendarteritis Obliterans Pulmonalis. Deutsches Arch. f. klin. Med. 180: 645, 1937.

Four cases are described. In this disease the involvement starts in the smallest pulmonary arteries and spreads centrally. The histologic picture in the arteries is typical of the thromboendarteritis obliterans elsewhere. There is hypertrophy and dilatation of the right ventricle. Clinically there is circulatory failure, edema, cyanosis, and dyspnea. The lungs appear to be normal.

KATZ.

Wood, William B., and Janeway, Charles A.: Change in Plasma Volume During Recovery from Congestive Heart Failure. Arch. Int. Med. 62: 151, 1938.

Appreciable increases in the volume of packed red blood cells, hemoglobin value, red blood cell count, and plasma protein concentration have been observed for patients during recovery from severe congestive heart failure. These changes take place rapidly, within three to six days, and are interpreted as indicating a decrease in the volume of plasma. The possible relation between the decrease in plasma volume and the disappearance of cardiac edema is discussed.

AUTHOR.

Deppe, B., and Bierhaus, H.: The Dynamics of the Human Circulation During Exercise and the Recovery Phase. Arch. f. Kreislaufforsch. 2: 357, 1938.

During exercise on an ergometer with the subject lying horizontally, the dynamics were followed by recording simultaneously carotid and femoral pulse optically and blood pressure by auscultation. From these data the following were determined: the duration of the pulse, of systole, of diastole, and the pulse wave velocity in the aorta. The cross section area of the elastic reservoir was determined from Suter's tables. From these data the mean pressure, elastic resistance, the peripheral resistance, and the stroke volume were calculated. It was found that minute volumes, stroke volume, heart rate, elastic resistance, systolic pressure, and work of the heart were all increased during exercise. Diastolic pressure did not change and the peripheral resistance decreased. These changes are roughly proportional to the work done. The errors inherent in Broemser and Ranke's and Wezler and Böger's formulas for calculating work are compared.

KATZ.

Heymans, Corneille: The Pressoreceptive Mechanisms for the Regulation of Heart Rate, Vasomotor Tone, Blood Pressure and Blood Supply. New England J. Med. 219: 147, 1938.

The heart rate, vasomotor tone, blood pressure, and blood supply are regulated by a number of pressoreceptive areas, the most important of which are the carotid sinus and aortic arch. Other areas provided with reflexogenic sensitivity are the left auricle and ventricle, the thoracic and mesenteric arteries, the venae cavae and right auricle and the pulmonary artery.

The role of these mechanisms of cardiovascular regulation in the mechanism of circulatory collapse and in the adaptation of blood flow and blood supply to various areas is described.

NAIDE.

Stewart, Harold J., Deitrick, John E., Crane, Norman F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to (Part I) Rhythms Associated with Rapid Ventricular Rate and to (Part II) Rhythms Associated with Slow Ventricular Rate. J. Clin. Investigation 17: 449, 1938.

The rapid regular and irregular rhythms in human beings at rest are associated with marked decrease in functional capacity of the heart, as measured by cardiac output per minute and per beat and the work per beat. They were associated with the dilatation of the heart. They are very inefficient rhythms, the work of the left ventricle per beat not being commensurate with the size of the heart. As a consequence, in most instances they fall outside the zone of normal circulatory function. On the other hand, rhythms associated with slow ventricular rate, such as those illustrated by complete heart block, are not incompatible with a normal circulatory function when the subject is at rest. Patients suffering from these rhythms may exhibit lowering of the basal metabolic rate as a compensatory mechanism.

AUTHOR.

Porter, William B.: Differential Diagnosis of Traumatic Aneurysm and Arteriovenous Fistula. Am. J. M. Sc. 196: 75, 1938.

A technique is described for the positive differential diagnosis of traumatic aneurysm and arteriovenous fistula, and three illustrative cases are discussed.

The differential diagnosis in Case 1 was impossible with the use of the usual methods employed in the examination of patients with traumatic aneurysm and arteriovenous fistula. Normal venous pressure and velocity of blood flow in each arm were positive data favoring traumatic aneurysm, the diagnosis confirmed at operation.

Case 2 was most confusing. The history of local trauma, dilated regional veins, and the pulsating tumor in the popliteal space were findings common to both aneurysm and arteriovenous fistula. The aortic lesion resulting in changes in heart size, blood pressure, and pulse rate similar to those seen in arteriovenous fistula further confused the differential diagnosis. The venous pressure and velocity of blood flow were slightly lower on the side of the lesion. The difference was not significant and was accounted for by partial compression of the popliteal vein by the aneurysmal sac.

Case 3 illustrates typically the changes in venous pressure and velocity of blood flow occurring in arteriovenous fistula. The failure of compression to completely restore to normal the venous pressure and rate of blood flow is probably due to the collateral circulation around the fistulous connection. Extensive collateral circulation was demonstrated at the time of the operation, and it is felt that this technique of study may be an index to the degree of collateral blood flow and, therefore, a useful guide to the safety of surgical resection of the connecting artery and vein.

AUTHOR.

Allen, Frederick M.: The Tourniquet and Local Asphyxia. Am. J. Surg. 41: 192, 1938.

The effects of tourniquet constriction are (1) local and (2) constitutional.

1. The local effects are due to: (a) Direct pressure damage in the zone of ligation, influenced largely by the character of the tissue and the material, form, and tightness of the ligature. Contrary to the prevailing view, the evidence indicates that narrow rubber bands or tubes are less harmful and painful than broad tourniquets.

This direct pressure injury is probably more responsible for such aftereffects as contractures and permanent paralyses than the temporary tissue asphyxia, and it is partly avoidable. (b) Local asphyxia, which can be endured for much longer periods than commonly supposed, up to fifteen hours in experimental animals, and probably for this time or even longer in man. The different viscera can withstand various shorter periods of lack of blood. These survival periods are shortened by vascular disease, infection, and especially by heat.

2. The constitutional effects represent a form of secondary shock which is of clinical and experimental importance. While the physical theory of fluid migration is well supported by facts, it appears inadequate as an etiological explanation without the assumption of a toxic factor. The experiments modify the prevalent idea of vascular permeability in shock by suggesting also a special avidity of the tissues for fluid. Likewise the special benefit of transfusions exists only within narrow limits. In general the greatest aid in shock is the injection of very abundant saline solutions beginning at the earliest possible stage.

AUTHOR.

Mackey, W. Arthur, and Scott, Lawrence, W.: Treatment of Apoplexy by Infiltration of the Stellate Ganglion With Novocain. Brit. M. J. 2: 4043, 1938.

Ten patients in coma as the result of recent cerebrovascular accidents were treated by infiltrating the area of the stellate ganglion with a 1 per cent solution of novocain. Six of the patients had right hemiplegias and four left hemiplegias. In nineteen injections Horner's syndrome was produced fourteen times, and in nine of these immediate improvement in hemiparesis was manifest. In only one case, however, was the change dramatic. This was a young man with subacute bacterial endocarditis who, treated two hours after loss of consciousness, had immediate return of his full intellectual capacities. There was no evidence of any permanent benefit in any of the cases. Six patients died and four were dismissed from hospital with residual signs.

One patient developed respiratory paralysis immediately after the injection and required artificial respiration for one-half hour. It was believed to be due to entrance of some of the solution into a vein. No evidence of harm from the theoretically possible increased bleeding was encountered. The authors have suggested that further cases, particularly those of cerebral embolism, be studied before the method is rejected as worthless.

If improvement of cerebral function may be taken as a sign of release of spasm, the results of the procedure indicate that the cerebral vessels may react to embolic or thrombotic closure in a manner similar to that of the peripheral arteries. Although little may be added therapeutically, further treatment of apoplexy by injection of stellate ganglions and also by intravenous injections of papaverine should yield observations of value.

HINES.

Book Review

THE BIOLOGY OF ARTERIOSCLEROSIS. By M. C. Winternitz, M.D., R. M. Thomas, M.D., and P. M. LeCompte, M.D. Springfield, 1938, Charles C. Thomas, 139 pages, 116 illustrations.

The directive idea which guided these studies was the assumption that blood extravasated within the wall, especially in the intima, of the aorta and large arteries may be at least one source of the lipoidal deposit and the cause of the formation of the atheromatous plaques which characterize human simple intimal arteriosclerosis. The idea is based on the knowledge that lipoidal deposits at other sites may have their origin in extravasated blood, and the frequent observation of vascularization and hemorrhage within the lesions of human simple intimal arteriosclerosis. It is recognized by the authors that the mere demonstration of blood vessels and of extravasated blood in arteriosclerotic plaques does not constitute proof of a primary causal relationship between the former and the latter. The reverse may be true, for the vascularization and hemorrhage could be, as most students of the subject have thought, secondary to the lipoidal deposit. The authors' view has found support in their convincing demonstration by special technical methods of an "extensive vascular network" in the intima of normal blood vessels of a number of animal species other than man. The origin of the anastomosing intimal vasa has been demonstrated to be from three sources; namely, the adventitia, the region of orifices of branches, and directly from the lumen of the vessel. There are two outstanding weaknesses which must be explained before the significance of these studies can be fully recognized and the results applied to the problem of the origin of human simple arteriosclerosis. The first difficulty is that while the demonstration of anastomosing channels in the intima of normal arteries of different animal species can be accepted, yet it is a fact, which the authors fail to stress, that the arteriosclerosis which occurs in such animals is most commonly medial, characterized by degeneration and calcification of this coat and not by atheromatosis which is an important part of the lesion of human simple intimal arteriosclerosis. The second difficulty, the importance of which the authors fully recognize, is that they have failed to demonstrate anastomosing channels in the intima of normal human aorta and arteries; yet it is in this very location that simple arteriosclerosis develops in man. Until these obstacles are successfully overcome there can be no strict application of the results of this work to the complex problem of the pathogenesis of human simple arteriosclerosis. In any event, the authors have discovered many previously unknown facts about the vascularization of the walls of larger blood vessels and have developed or modified technical methods for such studies which should lead to valuable information. The book is well written; the bookmaking and reproduction of illustrations are excellent.

HARRY GOLDBLATT.

American Heart Association, Inc.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

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